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(54) Title: AQUEOUS GEL FORMULATIONS CONTAINING IMMUNE REPOSE MODIFIERS

(57) Abstract: Aqueous gel formulations, including an immune response modifier (IRM), such as those chosen from imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2 -bridged imidazoquinoline amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazonaphthyridine amines, thiazolonaphthyridine amines, pyrazolopyridine amines, pyrazoloquinoline amines, tetrahydropyrazoloquinoline amines, pyrazolonaphthyridine amines, tetrahydropyrazolonaphthyridine amines, and 1H-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, are provided. Methods of use and kits are also provided.

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## AQUEOUS GEL FORMULATIONS CONTAINING IMMUNE RESPONSE MODIFIERS

### CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of US provisional application 60/650030 filed on February 4, 2005.

### BACKGROUND

Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused  
cycloalkylimidazopyridine amine, 1,2-bridged imidazoquinoline amine, thiazoloquinoline  
amine, oxazoloquinoline amine, thiazolopyridine amine, oxazolopyridine amine,  
imidazonaphthyridine amine, imidazotetrahydronaphthyridine amine, and  
thiazolonaphthyridine amine compounds have demonstrated potent immunostimulating,  
antiviral and antitumor (including anticancer) activity, and have also been shown to be  
useful as vaccine adjuvants and for the treatment of TH2-mediated diseases. These  
compounds are hereinafter collectively referred to as "IRM" (immune response modifier)  
compounds.

The mechanism for the immunostimulatory activity of these IRM compounds is  
thought to be due in substantial part to enhancement of the immune response by induction  
of various important cytokines (e.g., interferons, interleukins, tumor necrosis factor, etc.).  
Such compounds have been shown to stimulate a rapid release of certain  
monocyte/macrophage-derived cytokines and are also capable of stimulating B cells to  
secrete antibodies, which play an important role in these IRM compounds' activities. One  
of the predominant immunostimulating responses to these compounds is the induction of  
interferon (IFN)- $\alpha$  production, which is believed to be very important in the acute antiviral  
and antitumor activities seen. Moreover, up regulation of other cytokines such as, for  
example, tumor necrosis factor (TNF), Interleukin-1 (IL-1), IL-6, and IL-12 also have  
potentially beneficial activities and are believed to contribute to the antiviral and antitumor  
properties of these compounds.

Although some of the beneficial effects of IRMs are known, the ability to provide  
therapeutic benefit via topical application of an IRM compound for treatment of a  
particular condition at a particular location may be hindered by a variety of factors. These

factors include irritation of the dermal or mucosal tissue to which the formulation is applied, ciliary clearance of the formulation, formulation wash away, insolubility and/or degradation of the IRM compound in the formulation, physical instability of the formulation (e.g., separation of components, thickening, precipitation/agglomeration of  
5 active ingredient, and the like), and poor permeation, for example. Accordingly, there is a continuing need for new methods and formulations to provide the greatest therapeutic benefit from this class of compounds.

### SUMMARY

10 The present invention is directed to aqueous gel formulations, kits, and methods of use. Herein, a "gel" is a composition that is substantially free of oil (and hence, is not a cream or a lotion). Preferably, gels of the present invention have a viscosity of at least 1000 Centipoise (cps) at room temperature (i.e., about 25°C). Preferably, gels of the present invention have a viscosity of no greater than 50,000 cps, and more preferably no  
15 greater than 30,000 cps.

Aqueous gels are not easily formed using certain IRMs due to the low intrinsic aqueous solubility of the free base (typically, less than 500 µg at 25°C). As a result, a cosolvent is typically used or a salt of the IRM is prepared in situ. This can result in the need for negatively charged thickeners, particularly two negatively charged thickeners, to  
20 provide the desirable viscosity. In preferred embodiments of the present invention, the negatively charged thickeners are not covalently bonded to the IRM.

In one embodiment, such aqueous gels include: water; an immune response modifier (IRM) other than 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine; a pharmaceutically acceptable acid; a water-miscible cosolvent; and a thickener  
25 system including a negatively charged thickener; wherein the aqueous gel has a viscosity of at least 1000 cps at 25°C.

In one embodiment, such aqueous gels are prepared by a method that includes combining components including: water; an immune response modifier (IRM) other than 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, or a salt thereof; a  
30 water-miscible cosolvent; and a thickener system including a negatively charged thickener; wherein the aqueous gel has a viscosity of at least 1000 cps at 25°C.

Gel formulations of the present invention can provide desirable vehicles for an IRM compound and can allow for easier manufacture and increased residence time of an IRM compound, particularly on dermal and/or mucosal tissue.

Furthermore, the use of negatively charged thickeners in the aqueous gels of the present invention reduces systemic exposure to the drug and hence reduces systemic levels of cytokines. This is desirable for many conditions for which treatment at a particular location (e.g., cervical dysplasia) is preferred. The use of a combination of negatively charged thickeners (i.e., at least two) is desirable when higher levels of cosolvents are used due to the low solubility of the drug (whether in free base or salt form) in water. This results in an aqueous gel that reduces systemic exposure and is physically stable.

In certain embodiments, the immune response modifier is selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinolines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; pyrazolopyridine amines; pyrazoloquinoline amines; tetrahydropyrazoloquinoline amines; pyrazolonaphthyridine amines; tetrahydropyrazolonaphthyridine amines; 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines; and combinations thereof.

The present invention also provides methods of using the formulations of the present invention. In one embodiment, the present invention provides a method for delivering an IRM compound to mucosal tissue of a subject, the method including applying an aqueous gel of the present invention. Preferably, the mucosal tissue is associated with a condition selected from the group consisting of a cervical dysplasia, a papilloma virus infection of the cervix, a low-grade squamous intraepithelial lesion, a high-grade squamous intraepithelial lesion, atypical squamous cells of undetermined significance, a cervical intraepithelial neoplasia, an atopic allergic response, allergic rhinitis, a neoplastic lesion, and a premalignant lesion.

In another method, the aqueous gels of the present invention can be used to treat a dermal and/or mucosal condition in a subject in need thereof. The method includes applying an aqueous gel of the invention to the affected area of the subject. The present



invention also provides kits that include a barrel type applicator and an aqueous gel of the present invention, which can be in a separate container or prefilled in the barrel type applicator.

The terms "comprises" and variations thereof do not have a limiting meaning  
5 where these terms appear in the description and claims.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably. Thus, for example, an aqueous formulation that comprises "an" immune response modifier can be interpreted to mean that the formulation includes "one or more" immune response modifiers. Similarly, a formulation comprising "a" preservative can be  
10 interpreted to mean that the formulation includes "one or more" preservatives.

Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description  
15 that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

## 20 DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention provides aqueous gel formulations, kits, and methods of use. Such gels are compositions that are substantially free of oil (and hence, they are not creams or lotions). Preferably, gels of the present invention have a viscosity of at least 1000 Centipoise (cps) at 25°C. Preferably, gels of the present invention have a viscosity  
25 of no greater than 50,000 cps, and more preferably no greater than 30,000 cps.

In one embodiment, such aqueous gels include: water; an immune response modifier (IRM) other than 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine; a pharmaceutically acceptable acid; a water-miscible cosolvent; and a thickener system including a negatively charged thickener (preferably, at least two negatively  
30 charged thickeners, which are typically of different charge density); wherein the aqueous gel has a viscosity of at least 1000 cps at 25°C.

In one embodiment, such aqueous gels are prepared by a method that includes combining components including: water; an immune response modifier (IRM) other than 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, or a salt thereof; a water-miscible cosolvent; and a thickener system including a negatively charged thickener (preferably, at least two negatively charged thickeners, which are typically of different charge density); wherein the aqueous gel has a viscosity of at least 1000 cps at 25°C.

The immune response modifier is substantially completely dissolved at a therapeutic level (i.e., therapeutically effective amount) in the formulation at room temperature. This amount is effective to treat and/or prevent a specified condition. In general, the amount of IRM present in an aqueous gel formulation of the invention will be an amount effective to provide a desired physiological effect, e.g., to treat a targeted condition (e.g., reduce symptoms of allergic rhinitis), to prevent recurrence of the condition, or to promote immunity against the condition. For certain embodiments, an amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more manifestations of viral infections, such as viral load, rate of virus production, or mortality as compared to untreated control animals.

In certain methods of the present invention, the mucosal tissue is associated with a condition selected from the group consisting of a cervical dysplasia, a papilloma virus infection of the cervix, a low-grade squamous intraepithelial lesion, a high-grade squamous intraepithelial lesion, atypical squamous cells of undetermined significance, a cervical intraepithelial neoplasia, an atopic allergic response, allergic rhinitis, a neoplastic lesion, and a premalignant lesion.

In certain methods of the present invention, the mucosal tissue is on the cervix and the associated condition is selected from the group consisting of cervical dysplasia, high-grade squamous intraepithelial lesions, low-grade squamous intraepithelial lesions, and atypical squamous cells of undetermined significance with the presence of high risk HPV.

In certain methods of the present invention, the mucosal tissue is on the cervix and the associated condition is atypical squamous cells of undetermined significance with the presence of high risk HPV.

In certain methods of the present invention, the mucosal tissue is on the cervix and the associated condition is a papilloma virus infection of the cervix.

The amount of IRM compound that will be therapeutically effective in a specific situation will depend on such things as the dosing regimen, the application site, the particular formulation and the condition being treated. As such, it is generally not practical to identify specific administration amounts herein; however, those skilled in the art will be able to determine appropriate therapeutically effective amounts based on the guidance provided herein, information available in the art pertaining to these compounds, and routine testing.

In some embodiments, the methods of the present invention include administering sufficient formulation to provide a dose of an IRM compound of, for example, from 100 ng/kg to 50 mg/kg to the subject, although in some embodiments the methods may be performed by administering an IRM compound in concentrations outside this range. In some of these embodiments, the method includes administering sufficient formulation to provide a dose of an IRM compound of from 10 µg/kg to 5 mg/kg to the subject, for example, a dose of from 100 µg/kg to 1 mg/kg.

In certain embodiments of the formulations of the invention, the amount or concentration of an IRM compound is at least 0.0001% by weight (wt-%), in other embodiments, at least 0.001 wt-%, in other embodiments at least 0.01 wt-%, and in other embodiments at least 0.1 wt-%, based on the total weight of the aqueous gel. In certain embodiments, the amount of an IRM compound is no greater than 7 wt-%, in other embodiments no greater than 5 wt-%, in other embodiments no greater than 3 wt-%, in other embodiments no greater than 2 wt-%, and in other embodiments no greater than 1 wt-%, based on the total weight of the aqueous gel.

One or more IRM compounds may be present in the formulation as the sole therapeutically active ingredient or in combination with other therapeutic agents. Such other therapeutic agents may include, for example, antibiotics, such as penicillin or tetracycline, corticosteroids, such as hydrocortisone or betamethasone, nonsteroidal antiinflammatories, such as flurbiprofen, ibuprofen, or naproxen, or antivirals, such as acyclovir or valcyclovir.

In some embodiments, the above-described formulations are particularly advantageous for application for a period of time sufficient to obtain a desired therapeutic effect without undesired systemic absorption of the IRM compound.

The IRM of the present invention is present in the gel formulations in combination with a pharmaceutically acceptable acid. Such acid is preferably present in a stoichiometric amount relative to the IRM.

A wide range of pharmaceutically acceptable acids can be used to form salts of IRMs. Examples of such acids are described in Berge et al., J. Pharm. Sciences, 66, 1-19 (1977). Preferred pharmaceutically acceptable acids (e.g., suitable for incorporation in the gels of the present invention or for forming salts of the IRM of the present invention) include, for example, an alkylsulfonic acid, an arylsulfonic acid, a carboxylic acid, a halo acid, sulfuric acid, phosphoric acid, a dicarboxylic acid, a tricarboxylic acid, and combinations thereof. More preferred pharmaceutically acceptable acids include acetic acid, hydrobromic acid, hydrochloric acid, D-gluconic acid, D- and L-lactic acid, methanesulfonic acid, ethanesulfonic acid, propionic acid, benzenesulfonic acid, citric acid, phosphoric acid, succinic acid, sulfuric acid, D- and L-tartaric acid, *p*-toluenesulfonic acid, and combinations thereof. Particularly preferred salts of the IRM are alkylsulfonate salts (e.g., ethanesulfonate or methanesulfonate).

An IRM compound, and salts thereof, described herein include any of their pharmaceutically acceptable forms, such as isomers (e.g., diastereomers and enantiomers), solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes the use of each of the compound's enantiomers as well as racemic combinations of the enantiomers. Also, if a salt is optically active, the invention specifically includes the use of each of the salt's enantiomers as well as racemic combinations of the enantiomers.

### IRM Compounds

Preferred IRM compounds suitable for use in the formulations of the invention preferably include compounds having a 2-aminopyridine fused to a five membered nitrogen-containing heterocyclic ring. Other small organic molecules known to function as IRM compounds are also suitable for use in the formulations of the invention.

Certain IRMs are small organic molecules (e.g., molecular weight under about 1000 Daltons, preferably under about 500 Daltons, as opposed to large biologic protein, peptides, and the like) such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640; 5,446,153; 5,482,936;

5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,541,485;  
6,545,016; 6,545,017; 6,573,273; 6,656,938; 6,660,735; 6,660,747; 6,664,260; 6,664,264;  
6,664,265; 6,667,312; 6,670,372; 6,677,347; 6,677,348; 6,677,349; 6,683,088; 6,756,382;  
6,797,718; and 6,818,650; U.S. Patent Publication Nos. 2004/0091491; 2004/0147543;  
5 and 2004/0176367; and International Publication Nos. WO 2005/18551, WO 2005/18556,  
WO 2005/20999, WO 2005/032484, WO 2005/048933, WO 2005/048945, WO  
2005/051317, WO 2005/051324, WO 2005/066169, WO 2005/066170, WO 2005/066172,  
WO 2005/076783, WO 2005/079195, and WO2005/094531.

IRM compounds suitable for use in the invention preferably include compounds  
10 having a 2-aminopyridine fused to a five membered nitrogen-containing heterocyclic ring.  
Such compounds include, for example, imidazoquinoline amines including but not limited  
to substituted imidazoquinoline amines such as, for example, amide substituted  
imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea  
substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines,  
15 heterocyclic ether substituted imidazoquinoline amines, amido ether substituted  
imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea  
substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines,  
hydroxylamine substituted imidazoquinoline amines, oxime substituted imidazoquinoline  
amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted  
20 imidazoquinoline amines, and imidazoquinoline diamines; tetrahydroimidazoquinoline  
amines including but not limited to amide substituted tetrahydroimidazoquinoline amines,  
sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted  
tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline  
amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether  
25 substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted  
tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers,  
thioether substituted tetrahydroimidazoquinoline amines, hydroxylamine substituted  
tetrahydroimidazoquinoline amines, oxime substituted tetrahydroimidazoquinoline  
amines, and tetrahydroimidazoquinoline diamines; imidazopyridine amines including but  
30 not limited to amide substituted imidazopyridine amines, sulfonamide substituted  
imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted  
imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido



ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, and thioether substituted imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines;  
5 oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; pyrazolopyridine amines; pyrazoloquinoline amines; tetrahydropyrazoloquinoline amines; pyrazolonaphthyridine amines; tetrahydropyrazolonaphthyridine amines; and 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines,  
10 naphthyridine amines, or tetrahydronaphthyridine amines.

In certain embodiments of the present invention, the IRM is an imidazoquinoline amine.

In certain embodiments of the present invention, the IRM is 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (imiquimod).

15 In certain embodiments of the present invention, the IRM is 2-propylthiazolo[4,5-*c*]quinolin-4-amine.

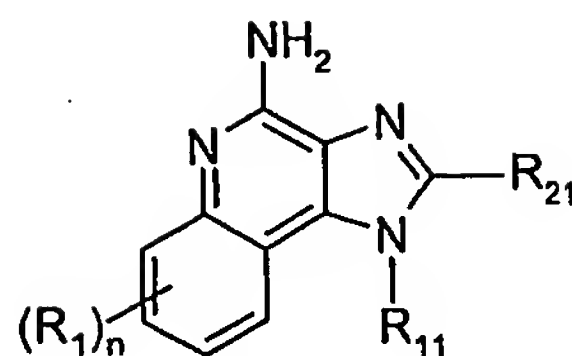
In certain embodiments of the present invention, IRM is an amide substituted imidazoquinoline amine. Preferably, the IRM is selected from the group consisting of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide, *N*-[2-(4-amino-7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]acetamide,  
20 and 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylbutyramide.

In certain embodiments of the present invention, the IRM is *N*-[2-(4-amino-7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]acetamide.

In certain embodiments of the present invention, the IRM is a urea substituted  
25 imidazoquinoline amine. Preferably, the IRM is *N*-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-*N'*-isopropylurea.

### Exemplary IRM Compounds

In certain embodiments of the present invention the IRM compound can be chosen  
30 from 1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by one of Formulas I-V below:



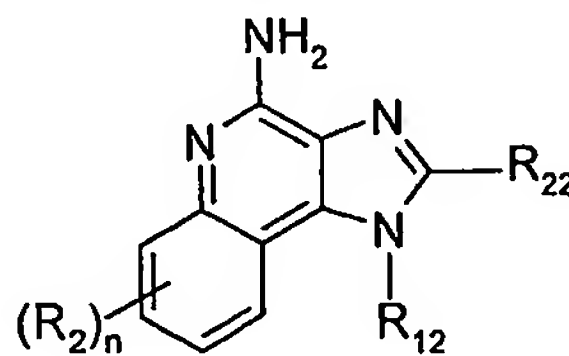
I

wherein

R<sub>11</sub> is selected from alkyl of one to ten carbon atoms, hydroxyalkyl of one to six  
 5 carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four  
 carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms,  
 benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being  
 optionally substituted on the benzene ring by one or two moieties independently selected  
 from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen,  
 10 with the proviso that if said benzene ring is substituted by two of said moieties, then said  
 moieties together contain no more than six carbon atoms;

R<sub>21</sub> is selected from hydrogen, alkyl of one to eight carbon atoms, benzyl,  
 (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally  
 substituted on the benzene ring by one or two moieties independently selected from alkyl  
 15 of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the  
 proviso that when the benzene ring is substituted by two of said moieties, then the  
 moieties together contain no more than six carbon atoms; and

each R<sub>1</sub> is independently selected from alkoxy of one to four carbon atoms,  
 halogen, and alkyl of one to four carbon atoms, and n is an integer from 0 to 2, with the  
 20 proviso that if n is 2, then said R<sub>1</sub> groups together contain no more than six carbon atoms;



II

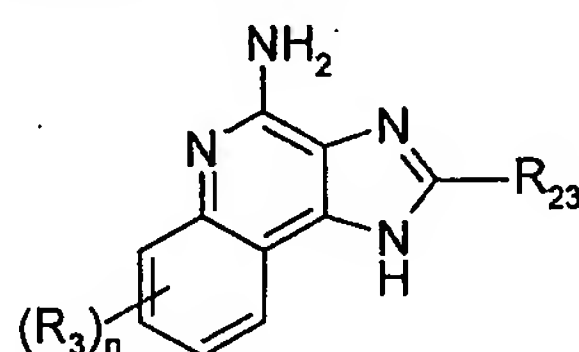
wherein

R<sub>12</sub> is selected from straight chain or branched chain alkenyl containing two to ten  
 25 carbon atoms and substituted straight chain or branched chain alkenyl containing two to  
 ten carbon atoms, wherein the substituent is selected from straight chain or branched chain

alkyl containing one to four carbon atoms and cycloalkyl containing three to six carbon atoms; and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; and

$R_{22}$  is selected from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from straight chain or branched chain alkyl containing one to four carbon atoms, straight chain or branched chain alkoxy containing one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each  $R_2$  is independently selected from straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms, and  $n$  is an integer from zero to 2, with the proviso that if  $n$  is 2, then said  $R_2$  groups together contain no more than six carbon atoms;

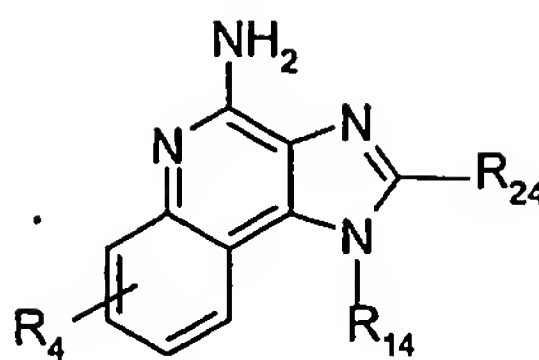


III

wherein

$R_{23}$  is selected from hydrogen, straight chain or branched chain alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from straight chain or branched chain alkyl of one to four carbon atoms, straight chain or branched chain alkoxy of one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each  $R_3$  is independently selected from straight chain or branched chain alkoxy of one to four carbon atoms, halogen, and straight chain or branched chain alkyl of one to four carbon atoms, and  $n$  is an integer from zero to 2, with the proviso that if  $n$  is 2, then said  $R_3$  groups together contain no more than six carbon atoms;



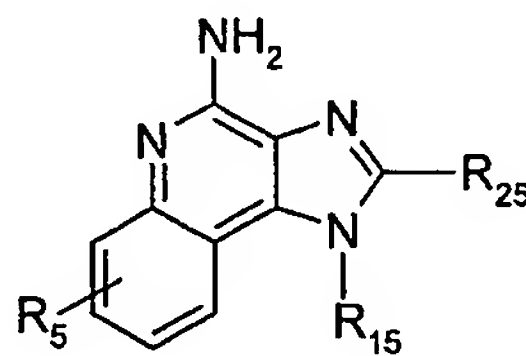
IV

wherein

$R_{14}$  is  $-\text{CHR}_x\text{R}_y$  wherein  $\text{R}_y$  is hydrogen or a carbon-carbon bond, with the proviso  
 5 that when  $\text{R}_y$  is hydrogen  $\text{R}_x$  is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further proviso that when  $\text{R}_y$  is a carbon-carbon bond  $\text{R}_y$  and  $\text{R}_x$  together form a tetrahydrofuranyl  
 10 group optionally substituted with one or more substituents independently selected from hydroxy and hydroxyalkyl of one to four carbon atoms;

$\text{R}_{24}$  is selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen; and

15  $\text{R}_4$  is selected from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;



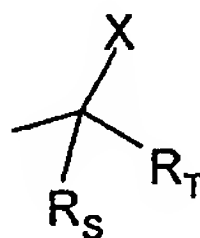
V

20 wherein

$\text{R}_{15}$  is selected from hydrogen; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is selected from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted  
 25 by straight chain or branched chain alkyl containing one to four carbon atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted

straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl  
 5 wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties  
 10 independently selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

R<sub>25</sub> is



15 wherein

R<sub>S</sub> and R<sub>T</sub> are independently selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

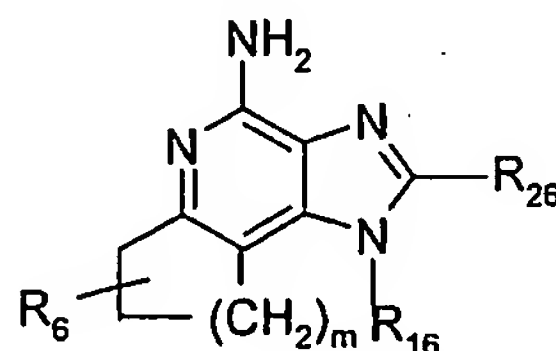
X is selected from alkoxy containing one to four carbon atoms, alkoxyalkyl  
 20 wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, hydroxyalkyl of one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, chloro, hydroxy, 1-morpholino, 1-pyrrolidino, alkylthio of one  
 25 to four carbon atoms; and

R<sub>S</sub> is selected from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;

and pharmaceutically acceptable salts of any of the foregoing.



In another embodiment, the IRM compound can be chosen from 6,7 fused cycloalkylimidazopyridine amines defined by Formula VI below:



VI

5 wherein

m is 1, 2, or 3;

R<sub>16</sub> is selected from hydrogen; cyclic alkyl of three, four, or five carbon atoms; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the  
 10 substituent is selected from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; fluoro- or chloroalkyl containing from one to ten carbon atoms and one or more fluorine or chlorine atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched  
 15 chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon  
 20 atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms, with the proviso that any such alkyl, substituted alkyl, alkenyl, substituted alkenyl, hydroxyalkyl, alkoxyalkyl, or acyloxyalkyl group does not have a fully carbon substituted carbon atom bonded directly to the nitrogen atom; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by  
 25 one or two moieties independently selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms; and -CHR<sub>x</sub>R<sub>y</sub>

wherein

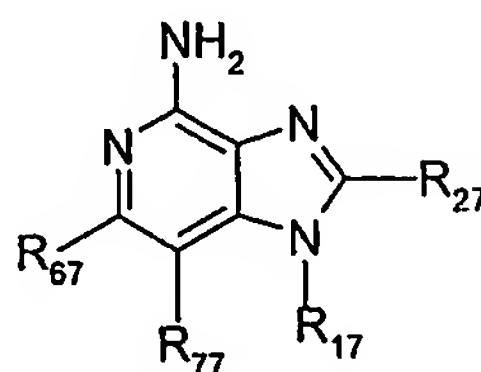
$R_y$  is hydrogen or a carbon-carbon bond, with the proviso that when  $R_y$  is hydrogen  $R_x$  is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, 2-, 3-, or 4-pyridyl, and with the further proviso that when  $R_y$  is a carbon-carbon bond  $R_y$  and  $R_x$  together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from hydroxy and hydroxyalkyl of one to four carbon atoms;

10  $R_{26}$  is selected from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; morpholinoalkyl; benzyl; (phenyl)ethyl; and phenyl, the benzyl, (phenyl)ethyl, or phenyl substituent being optionally substituted on the benzene ring by a moiety selected from methyl, methoxy, and halogen; and  $-C(R_S)(R_T)(X)$  wherein  $R_S$  and  
15  $R_T$  are independently selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

$X$  is selected from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety  
20 contains one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, alkylthio of one to four carbon atoms, and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms; and

25  $R_6$  is selected from hydrogen, fluoro, chloro, straight chain or branched chain alkyl containing one to four carbon atoms, and straight chain or branched chain fluoro- or chloroalkyl containing one to four carbon atoms and at least one fluorine or chlorine atom; and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from imidazopyridine amines defined by Formula VII below:



VII

5 wherein

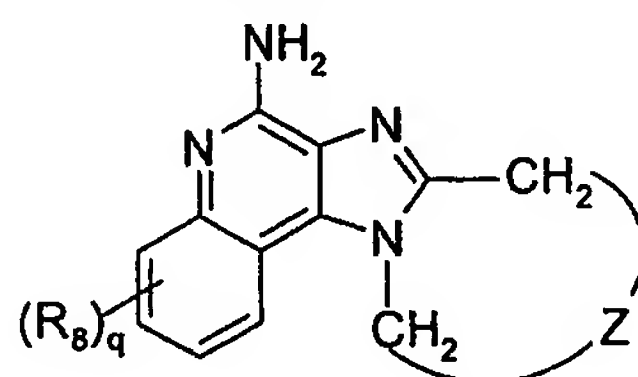
$R_{17}$  is selected from hydrogen;  $-CH_2R_w$  wherein  $R_w$  is selected from straight chain, branched chain, or cyclic alkyl containing one to ten carbon atoms, straight chain or branched chain alkenyl containing two to ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms, and phenylethyl; and  $-CH=CR_ZR_Z$  wherein each  $R_Z$  is independently straight chain, branched chain, or cyclic alkyl of one to six carbon atoms;

$R_{27}$  is selected from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl and phenyl being optionally substituted on the benzene ring by a moiety selected from methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms;

20  $R_{67}$  and  $R_{77}$  are independently selected from hydrogen and alkyl of one to five carbon atoms, with the proviso that  $R_{67}$  and  $R_{77}$  taken together contain no more than six carbon atoms, and with the further proviso that when  $R_{77}$  is hydrogen then  $R_{67}$  is other than hydrogen and  $R_{27}$  is other than hydrogen or morpholinoalkyl, and with the further proviso that when  $R_{67}$  is hydrogen then  $R_{77}$  and  $R_{27}$  are other than hydrogen;

25 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1,2 bridged imidazoquinoline amines defined by Formula VIII below:



VIII

5 wherein

Z is selected from

-(CH<sub>2</sub>)<sub>p</sub>- wherein p is 1 to 4;

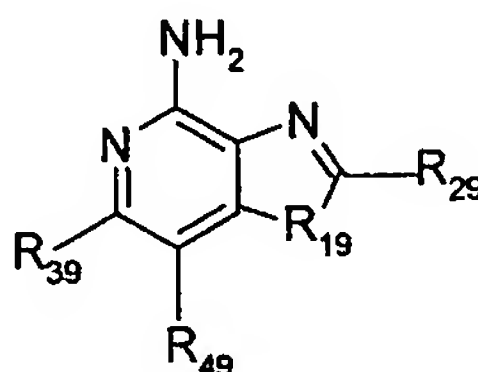
10 -(CH<sub>2</sub>)<sub>a</sub>-C(R<sub>D</sub>R<sub>E</sub>)(CH<sub>2</sub>)<sub>b</sub>-, wherein a and b are integers and a+b is 0 to 3, R<sub>D</sub> is hydrogen or alkyl of one to four carbon atoms, and R<sub>E</sub> is selected from alkyl of one to four carbon atoms, hydroxy, -OR<sub>F</sub> wherein R<sub>F</sub> is alkyl of one to four carbon atoms, and -NR<sub>G</sub>R'<sub>G</sub> wherein R<sub>G</sub> and R'<sub>G</sub> are independently hydrogen or alkyl of one to four carbon atoms; and

-(CH<sub>2</sub>)<sub>a</sub>-(Y)-(CH<sub>2</sub>)<sub>b</sub>- wherein a and b are integers and a+b is 0 to 3, and Y is O, S, or -NR<sub>J</sub>- wherein R<sub>J</sub> is hydrogen or alkyl of one to four carbon atoms;

15 q is 0 or 1; and

R<sub>8</sub> is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, and pharmaceutically acceptable salts thereof.

20 In another embodiment, the IRM compound can be chosen from thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, thiazolonaphthyridine amines and oxazolonaphthyridine amines defined by Formula IX below:



IX

25

wherein:

R<sub>19</sub> is selected from oxygen, sulfur and selenium;

R<sub>29</sub> is selected from

- hydrogen;
- alkyl;
- 5        -alkyl-OH;
- haloalkyl;
- alkenyl;
- alkyl-X-alkyl;
- alkyl-X-alkenyl;
- 10       -alkenyl-X-alkyl;
- alkenyl-X-alkenyl;
- alkyl-N(R<sub>59</sub>)<sub>2</sub>;
- alkyl-N<sub>3</sub>;
- alkyl-O-C(O)-N(R<sub>59</sub>)<sub>2</sub>;
- 15       -heterocyclyl;
- alkyl-X-heterocyclyl;
- alkenyl-X-heterocyclyl;
- aryl;
- alkyl-X-aryl;
- 20       -alkenyl-X-aryl;
- heteroaryl;
- alkyl-X-heteroaryl; and
- alkenyl-X-heteroaryl;

R<sub>39</sub> and R<sub>49</sub> are each independently:

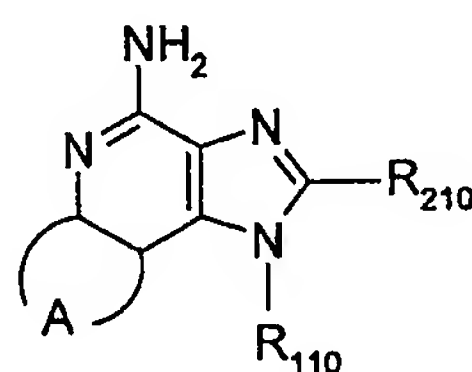
- 25       -hydrogen;
- X-alkyl;
- halo;
- haloalkyl;
- N(R<sub>59</sub>)<sub>2</sub>;
- 30       or when taken together, R<sub>39</sub> and R<sub>49</sub> form a fused  
aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;



X is selected from  $-O-$ ,  $-S-$ ,  $-NR_{59}-$ ,  $-C(O)-$ ,  $-C(O)O-$ ,  $-OC(O)-$ , and a bond;  
and

each  $R_{59}$  is independently H or  $C_{1-8}$ alkyl;  
and pharmaceutically acceptable salts thereof.

5 In another embodiment, the IRM compound can be chosen from  
imidazonaphthyridine amines and imidazotetrahydronaphthyridine amines defined by  
Formulas X and XI below:



X

10 wherein

A is  $=N-CR=CR-CR=$ ;  $=CR-N=CR-CR=$ ;  $=CR-CR=N-CR=$ ; or  
 $=CR-CR=CR-N=$ ;

$R_{110}$  is selected from:

- hydrogen;  
15 -  $C_{1-20}$  alkyl or  $C_{2-20}$  alkenyl that is unsubstituted or substituted by one or more  
substituents selected from:

-aryl;  
-heteroaryl;  
-heterocyclyl;  
20 -O- $C_{1-20}$  alkyl;  
-O-( $C_{1-20}$  alkyl) $_{0-1}$ -aryl;  
-O-( $C_{1-20}$  alkyl) $_{0-1}$ -heteroaryl;  
-O-( $C_{1-20}$  alkyl) $_{0-1}$ -heterocyclyl;  
-CO-O- $C_{1-20}$  alkyl;  
25 -S(O) $_{0-2}$ - $C_{1-20}$  alkyl;  
-S(O) $_{0-2}$ -( $C_{1-20}$  alkyl) $_{0-1}$ -aryl;  
-S(O) $_{0-2}$ -( $C_{1-20}$  alkyl) $_{0-1}$ -heteroaryl;  
-S(O) $_{0-2}$ -( $C_{1-20}$  alkyl) $_{0-1}$ -heterocyclyl;  
-N( $R_{310}$ ) $_2$ ;

-N<sub>3</sub>;

oxo;

-halogen;

-NO<sub>2</sub>;

5 -OH; and

-SH; and

-C<sub>1-20</sub> alkyl-NR<sub>310</sub>-Q-X-R<sub>410</sub> or -C<sub>2-20</sub> alkenyl-NR<sub>310</sub>-Q-X-R<sub>410</sub> wherein Q is -CO- or -SO<sub>2</sub>-; X is a bond, -O- or -NR<sub>310</sub>- and R<sub>410</sub> is aryl; heteroaryl; heterocyclyl; or -C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more substituents

10 selected from:

-aryl;

-heteroaryl;

-heterocyclyl;

-O-C<sub>1-20</sub> alkyl;

15 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;

-O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;

-O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;

-CO-O-C<sub>1-20</sub> alkyl;

-S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;

20 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;

-N(R<sub>310</sub>)<sub>2</sub>;

-NR<sub>310</sub>-CO-O-C<sub>1-20</sub> alkyl;

25 -N<sub>3</sub>;

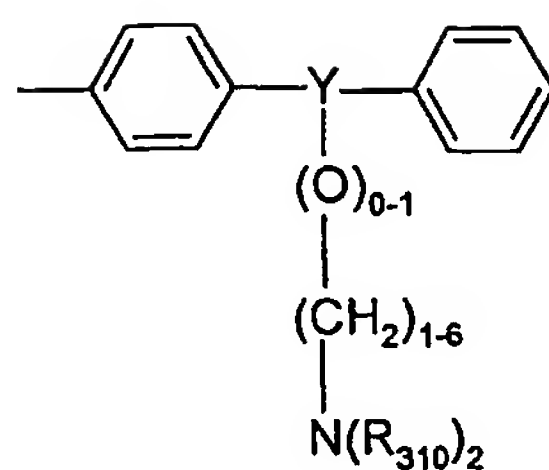
oxo;

-halogen;

-NO<sub>2</sub>;

-OH; and

30 -SH; or R<sub>410</sub> is



wherein Y is  $\text{---N---}$  or  $\text{---CR---}$ ;

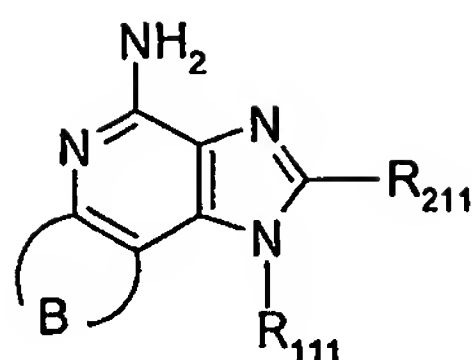
$\text{R}_{210}$  is selected from:

- hydrogen;
- 5       $\text{---C}_{1-10}$  alkyl;
- $\text{---C}_{2-10}$  alkenyl;
- aryl;
- $\text{---C}_{1-10}$  alkyl- $\text{O---C}_{1-10}$  alkyl;
- $\text{---C}_{1-10}$  alkyl- $\text{O---C}_{2-10}$  alkenyl; and
- 10       $\text{---C}_{1-10}$  alkyl or  $\text{C}_{2-10}$  alkenyl substituted by one or more substituents selected from:

- $\text{---OH}$ ;
- halogen;
- $\text{---N}(\text{R}_{310})_2$ ;
- 15       $\text{---CO---N}(\text{R}_{310})_2$ ;
- $\text{---CO---C}_{1-10}$  alkyl;
- $\text{---N}_3$ ;
- aryl;
- heteroaryl;
- 20      -heterocyclyl;
- $\text{---CO---aryl}$ ; and
- $\text{---CO---heteroaryl}$ ;

each  $\text{R}_{310}$  is independently selected from hydrogen and  $\text{C}_{1-10}$  alkyl; and

25      each R is independently selected from hydrogen,  $\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  alkoxy, halogen and trifluoromethyl;



XI

wherein

B is -NR-C(R)<sub>2</sub>-C(R)<sub>2</sub>-C(R)<sub>2</sub>-; -C(R)<sub>2</sub>-NR-C(R)<sub>2</sub>-C(R)<sub>2</sub>-;

5 -C(R)<sub>2</sub>-C(R)<sub>2</sub>-NR-C(R)<sub>2</sub>- or -C(R)<sub>2</sub>-C(R)<sub>2</sub>-C(R)<sub>2</sub>-NR-;

R<sub>111</sub> is selected from:

- hydrogen;

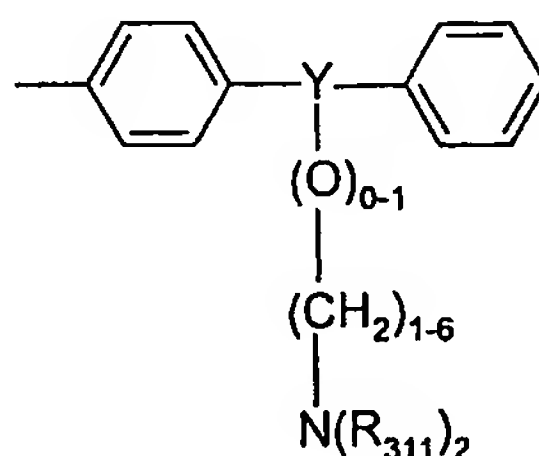
-C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more

substituents selected from:

- 10 -aryl;
- heteroaryl;
- heterocyclyl;
- O-C<sub>1-20</sub> alkyl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- 15 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- CO-O-C<sub>1-20</sub> alkyl;
- S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- 20 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- N(R<sub>311</sub>)<sub>2</sub>;
- N<sub>3</sub>;
- oxo;
- 25 -halogen;
- NO<sub>2</sub>;
- OH; and
- SH; and

$-C_{1-20}$  alkyl- $NR_{311}$ -Q-X- $R_{411}$  or  $-C_{2-20}$  alkenyl- $NR_{311}$ -Q-X- $R_{411}$  wherein Q is  $-CO-$  or  $-SO_2-$ ; X is a bond,  $-O-$  or  $-NR_{311}-$  and  $R_{411}$  is aryl; heteroaryl; heterocyclyl; or  $-C_{1-20}$  alkyl or  $C_{2-20}$  alkenyl that is unsubstituted or substituted by one or more substituents selected from:

- 5                     $-aryl$ ;
- $-heteroaryl$ ;
- $-heterocyclyl$ ;
- $-O-C_{1-20}$  alkyl;
- $-O-(C_{1-20} \text{ alkyl})_{0-1}-aryl$ ;
- 10                    $-O-(C_{1-20} \text{ alkyl})_{0-1}-heteroaryl$ ;
- $-O-(C_{1-20} \text{ alkyl})_{0-1}-heterocyclyl$ ;
- $-CO-O-C_{1-20}$  alkyl;
- $-S(O)_{0-2}-C_{1-20}$  alkyl;
- $-S(O)_{0-2}-(C_{1-20} \text{ alkyl})_{0-1}-aryl$ ;
- 15                    $-S(O)_{0-2}-(C_{1-20} \text{ alkyl})_{0-1}-heteroaryl$ ;
- $-S(O)_{0-2}-(C_{1-20} \text{ alkyl})_{0-1}-heterocyclyl$ ;
- $-N(R_{311})_2$ ;
- $-NR_{311}-CO-O-C_{1-20}$  alkyl;
- $-N_3$ ;
- 20                    $oxo$ ;
- $-halogen$ ;
- $-NO_2$ ;
- $-OH$ ; and
- $-SH$ ; or  $R_{411}$  is



25

wherein Y is  $-N-$  or  $-CR-$ ;

$R_{211}$  is selected from:

- $-hydrogen$ ;



-C<sub>1-10</sub> alkyl;  
 -C<sub>2-10</sub> alkenyl;  
 -aryl;  
 -C<sub>1-10</sub> alkyl -O-C<sub>1-10</sub>-alkyl;  
 5 -C<sub>1-10</sub> alkyl-O-C<sub>2-10</sub> alkenyl; and  
 -C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl substituted by one or more substituents selected from:

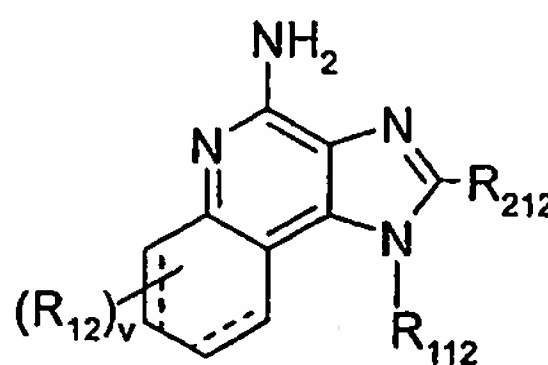
-OH;  
 -halogen;  
 10 -N(R<sub>311</sub>)<sub>2</sub>;  
 -CO-N(R<sub>311</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 15 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

each R<sub>311</sub> is independently selected from hydrogen and C<sub>1-10</sub> alkyl; and

20 each R is independently selected from hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, halogen, and trifluoromethyl;  
 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1H-imidazo[4,5-c]quinolin-4-amines and tetrahydro- 1H-imidazo[4,5-c]quinolin-4-amines defined by

25 Formulas XII, XIII and XIV below:



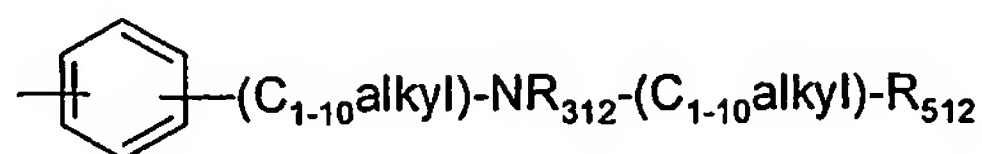
XII

wherein

$R_{112}$  is -alkyl- $NR_{312}$ -CO- $R_{412}$  or -alkenyl- $NR_{312}$ -CO- $R_{412}$  wherein  $R_{412}$  is aryl, heteroaryl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from:

- alkyl;
- 5        -alkenyl;
- alkynyl;
- (alkyl)<sub>0-1</sub>-aryl;
- (alkyl)<sub>0-1</sub>-(substituted aryl);
- (alkyl)<sub>0-1</sub>-heteroaryl;
- 10       -(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- O-alkyl;
- O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-(substituted aryl);
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- 15       -O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- CO-aryl;
- CO-(substituted aryl);
- CO-heteroaryl;
- CO-(substituted heteroaryl);
- 20       -COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
- 25       -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- P(O)(OR<sub>312</sub>)<sub>2</sub>;
- NR<sub>312</sub>-CO-O-alkyl;
- 30       -N<sub>3</sub>;
- halogen;
- NO<sub>2</sub>;

-CN;  
 -haloalkyl;  
 -O-haloalkyl;  
 -CO-haloalkyl;  
 5 -OH;  
 -SH; and in the case that R<sub>412</sub> is alkyl, alkenyl, or heterocyclyl, oxo;  
 or R<sub>412</sub> is



10 wherein R<sub>512</sub> is an aryl, (substituted aryl), heteroaryl, (substituted heteroaryl),  
 heterocyclyl or (substituted heterocyclyl) group;

R<sub>212</sub> is selected from:

-hydrogen;  
 -alkyl;  
 15 -alkenyl;  
 -aryl;  
 -(substituted aryl);  
 -heteroaryl;  
 -(substituted heteroaryl);  
 20 -heterocyclyl;  
 -(substituted heterocyclyl);  
 -alkyl-O-alkyl;  
 -alkyl-O-alkenyl; and  
 -alkyl or alkenyl substituted by one or more substituents selected  
 25 from:

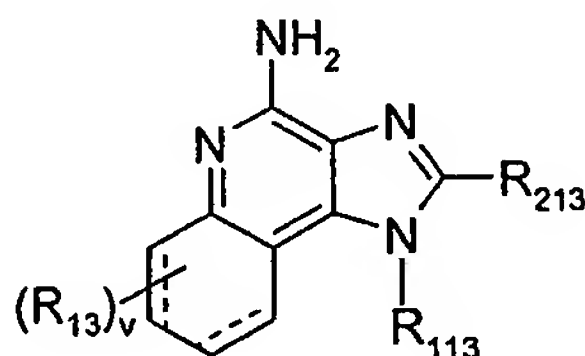
-OH;  
 -halogen;  
 -N(R<sub>312</sub>)<sub>2</sub>;  
 -CO-N(R<sub>312</sub>)<sub>2</sub>;  
 30 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;  
 -aryl;  
 -(substituted aryl);  
 -heteroaryl;  
 5 -(substituted heteroaryl);  
 -heterocyclyl;  
 -(substituted heterocyclyl);  
 -CO-aryl; and  
 -CO-heteroaryl;

10 each R<sub>312</sub> is independently selected from hydrogen; C<sub>1-10</sub> alkyl-heteroaryl; C<sub>1-10</sub> alkyl-(substituted heteroaryl); C<sub>1-10</sub> alkyl-aryl; C<sub>1-10</sub> alkyl-(substituted aryl) and C<sub>1-10</sub> alkyl;

v is 0 to 4;

and each R<sub>12</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 15 halogen, and trifluoromethyl;



XIII

wherein

20 R<sub>113</sub> is -alkyl-NR<sub>313</sub>-SO<sub>2</sub>-X-R<sub>413</sub> or -alkenyl-NR<sub>313</sub>-SO<sub>2</sub>-X-R<sub>413</sub>;

X is a bond or -NR<sub>513</sub>-;

R<sub>413</sub> is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from:

-alkyl;  
 25 -alkenyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -substituted cycloalkyl;

- substituted aryl;
- substituted heteroaryl;
- substituted heterocyclyl;
- O-alkyl;
- 5 -O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-substituted aryl;
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
- O-(alkyl)<sub>0-1</sub>-heterocyclyl;
- 10 -O-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
- COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;
- 15 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted aryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;
- 20 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>R<sub>313</sub>;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-O-alkyl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-alkyl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-aryl;
- 25 -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-substituted aryl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-heteroaryl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-substituted heteroaryl;
- N<sub>3</sub>;
- halogen;
- 30 -haloalkyl;
- haloalkoxy;
- CO-haloalkyl;

-CO-haloalkoxy;

-NO<sub>2</sub>;

-CN;

-OH;

5        -SH; and in the case that R<sub>413</sub> is alkyl, alkenyl, or heterocyclyl, oxo;

R<sub>213</sub> is selected from:

-hydrogen;

-alkyl;

-alkenyl;

10        -aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl-O-alkyl;

15        - alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected  
from:

-OH;

-halogen;

20        -N(R<sub>313</sub>)<sub>2</sub>;

-CO-N(R<sub>313</sub>)<sub>2</sub>;

-CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

25        -aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

30        -substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);



-CO-heteroaryl; and

-CO-(substituted heteroaryl);

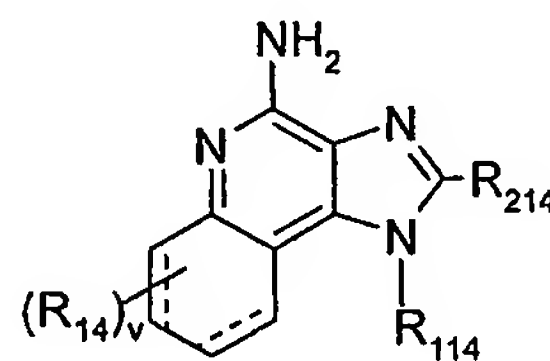
each  $R_{313}$  is independently selected from hydrogen and  $C_{1-10}$  alkyl; or when X is a bond  $R_{313}$  and  $R_{413}$  can join to form a 3 to 7 membered heterocyclic or substituted

5 heterocyclic ring;

$R_{513}$  is selected from hydrogen and  $C_{1-10}$  alkyl, or  $R_{413}$  and  $R_{513}$  can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

v is 0 to 4;

and each  $R_{13}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen, and trifluoromethyl;



XIV

wherein

15  $R_{114}$  is -alkyl- $NR_{314}$ -CY- $NR_{514}$ -X- $R_{414}$  or  
-alkenyl- $NR_{314}$ -CY- $NR_{514}$ -X- $R_{414}$

wherein

Y is =O or =S;

X is a bond, -CO- or -SO<sub>2</sub>-;

20  $R_{414}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from:

-alkyl;

-alkenyl;

-aryl;

25 -heteroaryl;

-heterocyclyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

- O-alkyl;  
-O-(alkyl)<sub>0-1</sub>-aryl;  
-O-(alkyl)<sub>0-1</sub>-substituted aryl;  
-O-(alkyl)<sub>0-1</sub>-heteroaryl;  
5 -O-(alkyl)<sub>0-1</sub>-substituted heteroaryl;  
-O-(alkyl)<sub>0-1</sub>-heterocyclyl;  
-O-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;  
-COOH;  
-CO-O-alkyl;  
10 -CO-alkyl;  
-S(O)<sub>0-2</sub>-alkyl;  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted aryl;  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
15 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heteroaryl;  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;  
-(alkyl)<sub>0-1</sub>-NR<sub>314</sub>R<sub>314</sub>;  
-(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-O-alkyl;  
20 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-alkyl;  
-(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-aryl;  
-(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-substituted aryl;  
-(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-heteroaryl;  
-(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-substituted heteroaryl;  
25 -N<sub>3</sub>;  
-halogen;  
-haloalkyl;  
-haloalkoxy;  
-CO-haloalkoxy;  
30 -NO<sub>2</sub>;  
-CN;  
-OH;

-SH; and, in the case that  $R_{414}$  is alkyl, alkenyl or heterocyclyl, oxo;  
with the proviso that when X is a bond  $R_{414}$  can additionally be hydrogen;

$R_{214}$  is selected from:

- hydrogen;
- 5        -alkyl;
- alkenyl;
- aryl;
- substituted aryl;
- heteroaryl;
- 10       -substituted heteroaryl;
- alkyl-O-alkyl;
- alkyl-O-alkenyl; and
- alkyl or alkenyl substituted by one or more substituents selected  
       from:
- 15       -OH;
- halogen;
- N( $R_{314}$ )<sub>2</sub>;
- CO-N( $R_{314}$ )<sub>2</sub>;
- CO-C<sub>1-10</sub> alkyl;
- 20       -CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- substituted aryl;
- heteroaryl;
- 25       -substituted heteroaryl;
- heterocyclyl;
- substituted heterocyclyl;
- CO-aryl;
- CO-(substituted aryl);
- 30       -CO-heteroaryl; and
- CO-(substituted heteroaryl);

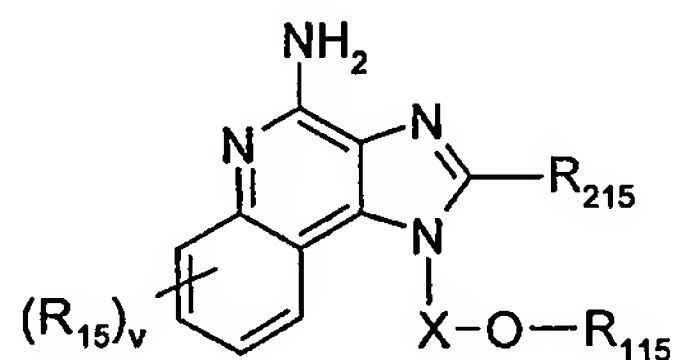
each  $R_{314}$  is independently selected from hydrogen and C<sub>1-10</sub> alkyl;

$R_{514}$  is selected from hydrogen and  $C_{1-10}$  alkyl, or  $R_{414}$  and  $R_{514}$  can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

$v$  is 0 to 4;

and each  $R_{14}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen, and trifluoromethyl; and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]quinolin-4-amines and tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by Formulas XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, and XXVI below:



XV

wherein:  $X$  is  $-\text{CHR}_{515}-$ ,  $-\text{CHR}_{515}\text{-alkyl-}$ , or  $-\text{CHR}_{515}\text{-alkenyl-}$ ;

$R_{115}$  is selected from:

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{—alkyl}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{—alkenyl}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{—aryl}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{—heteroaryl}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{—heterocyclyl}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{H}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{—alkyl}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{—alkenyl}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{—aryl}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{—heteroaryl}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{—heterocyclyl}$ ; and

$-R_{415}-NR_{715}-CR_{315}-R_{815}$ ;

Z is  $-NR_{515}-$ ,  $-O-$ , or  $-S-$ ;

$R_{215}$  is selected from:

-hydrogen;

5

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

10

-alkyl-Y-alkyl;

-alkyl-Y-alkenyl;

-alkyl-Y-aryl; and

-alkyl or alkenyl substituted by one or more substituents selected from:

15

-OH;

-halogen;

$-N(R_{515})_2$ ;

$-CO-N(R_{515})_2$ ;

$-CO-C_{1-10}$  alkyl;

20

$-CO-O-C_{1-10}$  alkyl;

$-N_3$ ;

-aryl;

-heteroaryl;

-heterocyclyl;

25

$-CO-aryl$ ; and

$-CO-heteroaryl$ ;

$R_{315}$  is  $=O$  or  $=S$ ;

$R_{415}$  is alkyl or alkenyl, which may be interrupted by one or more

$-O-$  groups;

30

each  $R_{515}$  is independently H or  $C_{1-10}$  alkyl;

$R_{615}$  is a bond, alkyl, or alkenyl, which may be interrupted by one or more  $-$

$O-$  groups;

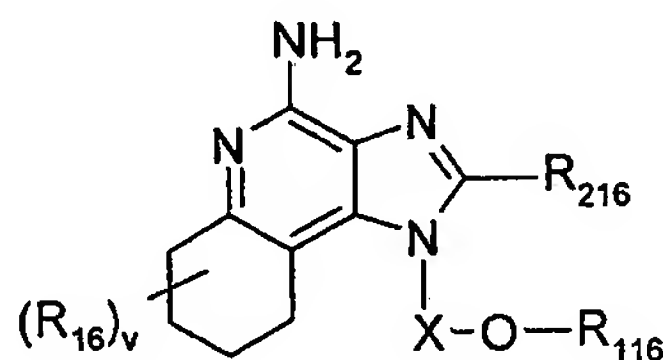
$R_{715}$  is H,  $C_{1-10}$  alkyl, or arylalkyl; or  $R_{415}$  and  $R_{715}$  can join together to form a ring;

$R_{815}$  is H or  $C_{1-10}$  alkyl; or  $R_{715}$  and  $R_{815}$  can join together to form a ring;

Y is  $-O-$  or  $-S(O)_{0-2}-$ ;

v is 0 to 4; and

each  $R_{15}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



XVI

wherein: X is  $-CHR_{516}-$ ,  $-CHR_{516}$ -alkyl-, or  $-CHR_{516}$ -alkenyl-;

$R_{116}$  is selected from:

$-R_{416}-CR_{316}-Z-R_{616}$ -alkyl;

$-R_{416}-CR_{316}-Z-R_{616}$ -alkenyl;

$-R_{416}-CR_{316}-Z-R_{616}$ -aryl;

$-R_{416}-CR_{316}-Z-R_{616}$ -heteroaryl;

$-R_{416}-CR_{316}-Z-R_{616}$ -heterocyclyl;

$-R_{416}-CR_{316}-Z-H$ ;

$-R_{416}-NR_{716}-CR_{316}-R_{616}$ -alkyl;

$-R_{416}-NR_{716}-CR_{316}-R_{616}$ -alkenyl;

$-R_{416}-NR_{716}-CR_{316}-R_{616}$ -aryl;

$-R_{416}-NR_{716}-CR_{316}-R_{616}$ -heteroaryl;

$-R_{416}-NR_{716}-CR_{316}-R_{616}$ -heterocyclyl; and

$-R_{416}-NR_{716}-CR_{316}-R_{816}$ ;

Z is  $-NR_{516}-$ ,  $-O-$ , or  $-S-$ ;

$R_{216}$  is selected from:

-hydrogen;

-alkyl;



- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- 5 -alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents selected from:
- 10 -OH;
- halogen;
- N(R<sub>516</sub>)<sub>2</sub>;
- CO-N(R<sub>516</sub>)<sub>2</sub>;
- CO-C<sub>1-10</sub> alkyl;
- 15 -CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- heteroaryl;
- heterocyclyl;
- 20 -CO-aryl; and
- CO-heteroaryl;

R<sub>316</sub> is =O or =S;

R<sub>416</sub> is alkyl or alkenyl, which may be interrupted by one or more

-O- groups;

25 each R<sub>516</sub> is independently H or C<sub>1-10</sub> alkyl;

R<sub>616</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

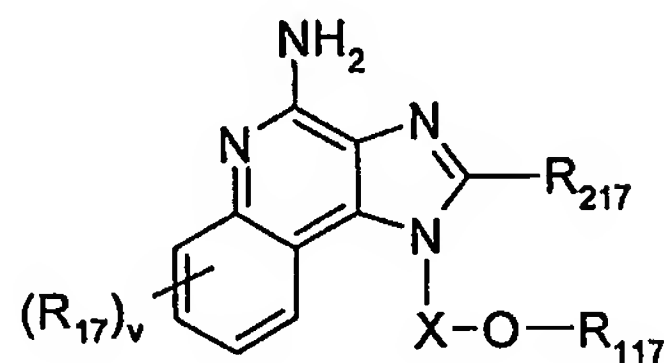
R<sub>716</sub> is H, C<sub>1-10</sub> alkyl, arylalkyl; or R<sub>416</sub> and R<sub>716</sub> can join together to form a ring;

30 R<sub>816</sub> is H or C<sub>1-10</sub> alkyl; or R<sub>716</sub> and R<sub>816</sub> can join together to form a ring;

Y is -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each  $R_{16}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



XVII

wherein: X is  $-\text{CHR}_{317}-$ ,  $-\text{CHR}_{317}\text{-alkyl}-$ , or  $-\text{CHR}_{317}\text{-alkenyl}-$ ;

$R_{117}$  is selected from:

- alkenyl;
- aryl; and
- $-\text{R}_{417}\text{-aryl}$ ;

$R_{217}$  is selected from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents selected from:

- OH;
- halogen;
- $-\text{N}(\text{R}_{317})_2$ ;
- $-\text{CO}-\text{N}(\text{R}_{317})_2$ ;
- $-\text{CO}-\text{C}_{1-10}\text{ alkyl}$ ;
- $-\text{CO}-\text{O}-\text{C}_{1-10}\text{ alkyl}$ ;

-N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

R<sub>417</sub> is alkyl or alkenyl, which may be interrupted by one or more

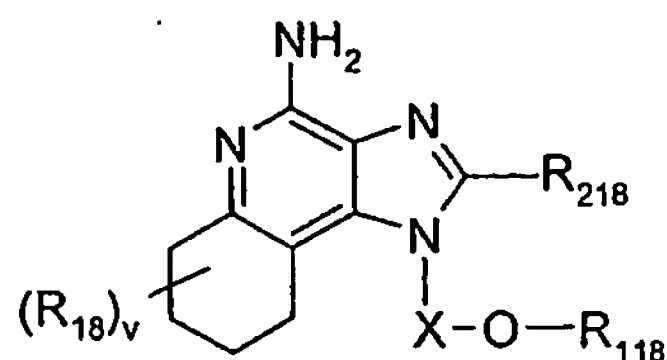
-O- groups;

each R<sub>317</sub> is independently H or C<sub>1-10</sub> alkyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each R<sub>17</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



XVIII

wherein: X is -CHR<sub>318</sub>-, -CHR<sub>318</sub>-alkyl-, or -CHR<sub>318</sub>-alkenyl-;

R<sub>118</sub> is selected from:

-aryl;  
 -alkenyl; and  
 -R<sub>418</sub>-aryl;

R<sub>218</sub> is selected from:

-hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;

-alkyl-Y-alkyl;  
 -alkyl-Y-aryl;  
 - alkyl-Y- alkenyl; and  
 - alkyl or alkenyl substituted by one or more substituents selected  
 from:

-OH;  
 -halogen;  
 -N(R<sub>318</sub>)<sub>2</sub>;  
 -CO-N(R<sub>318</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

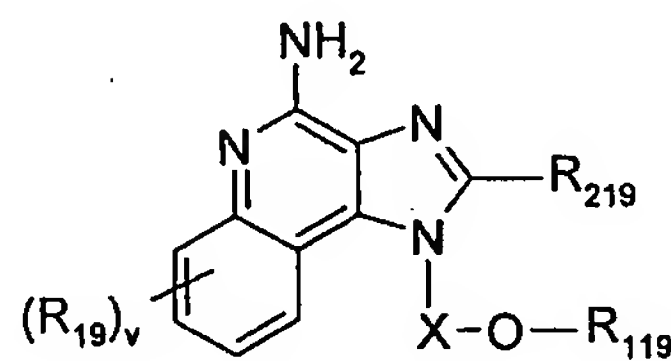
R<sub>418</sub> is alkyl or alkenyl, which may be interrupted by one or more  
 -O- groups;

each R<sub>318</sub> is independently H or C<sub>1-10</sub> alkyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each R<sub>18</sub> present is independently selected C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 hydroxy, halogen, and trifluoromethyl;



XIX

wherein: X is -CHR<sub>319</sub>-, -CHR<sub>319</sub>-alkyl-, or -CHR<sub>319</sub>-alkenyl-;

R<sub>119</sub> is selected from:

- heteroaryl;
- heterocyclyl;
- R<sub>419</sub>- heteroaryl; and
- R<sub>419</sub>-heterocyclyl;

R<sub>219</sub> is selected from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y- alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents selected from:

- OH;
- halogen;
- N(R<sub>319</sub>)<sub>2</sub>;
- CO-N(R<sub>319</sub>)<sub>2</sub>;
- CO-C<sub>1-10</sub> alkyl;
- CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- heteroaryl;
- heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

R<sub>419</sub> is alkyl or alkenyl, which may be interrupted by one or more

-O- groups;

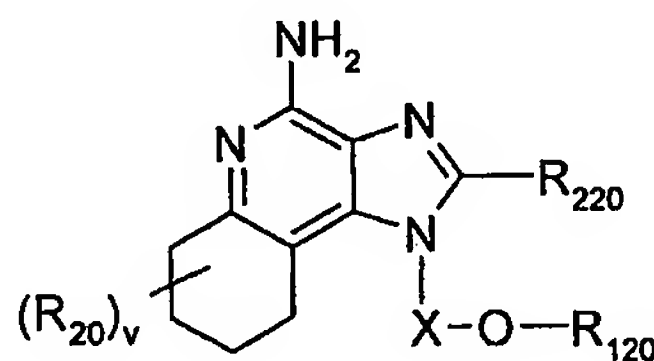
each R<sub>319</sub> is independently H or C<sub>1-10</sub> alkyl;

each Y is independently  $-O-$  or  $-S(O)_{0-2}-$ ;

v is 0 to 4; and

each  $R_{19}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;

5



XX

wherein: X is  $-CHR_{320}-$ ,  $-CHR_{320}-alkyl-$ , or  $-CHR_{320}-alkenyl-$ ;

10  $R_{120}$  is selected from:

-heteroaryl;

-heterocyclyl;

$-R_{420}-$  heteroaryl; and

$-R_{420}-$  heterocyclyl;

15  $R_{220}$  is selected from:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

20 -heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y-alkenyl;

-alkyl-Y-aryl; and

25 -alkyl or alkenyl substituted by one or more substituents selected from:

-OH;

-halogen;

$-N(R_{320})_2$ ;



-CO-N(R<sub>320</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

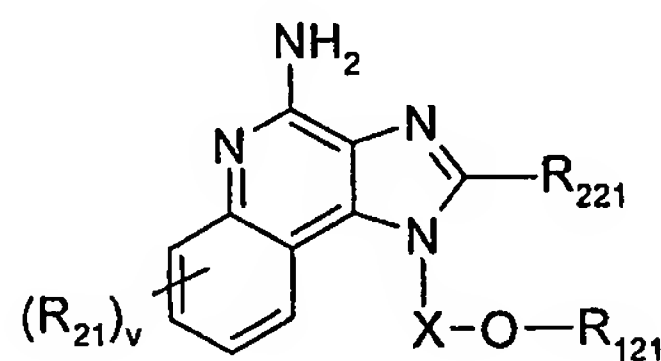
10 R<sub>420</sub> is alkyl or alkenyl, which may be interrupted by one or more  
 -O- groups;

each R<sub>320</sub> is independently H or C<sub>1-10</sub> alkyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

15 each R<sub>20</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 hydroxy, halogen, and trifluoromethyl;



XXI

20

wherein: X is -CHR<sub>521</sub>-, -CHR<sub>521</sub>-alkyl-, or -CHR<sub>521</sub>-alkenyl-;

R<sub>121</sub> is selected from:

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-alkyl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-alkenyl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-aryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-heteroaryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-heterocyclyl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>721</sub>;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-alkyl;

25

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-alkenyl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-aryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-heteroaryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-heterocyclyl; and  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NH<sub>2</sub>;

R<sub>221</sub> is selected from:

-hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -alkyl-Y-alkyl;  
 -alkyl-Y-alkenyl;  
 -alkyl-Y-aryl; and  
 -alkyl or alkenyl substituted by one or more substituents selected  
 from:

-OH;  
 -halogen;  
 -N(R<sub>521</sub>)<sub>2</sub>;  
 -CO-N(R<sub>521</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

Y is -O- or -S(O)<sub>0-2</sub>;

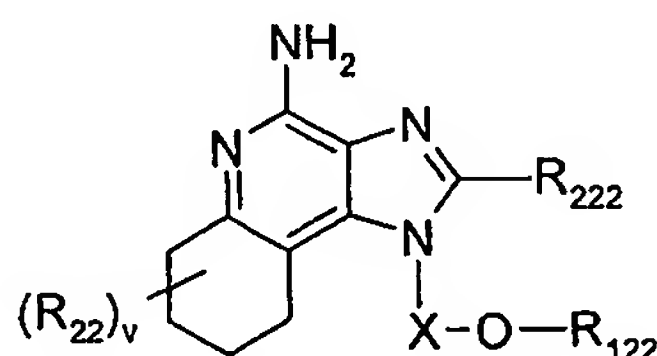
R<sub>321</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl;

each  $R_{421}$  is independently alkyl or alkenyl, which may be interrupted by one or more  $-O-$  groups; or  $R_{321}$  and  $R_{421}$  can join together to form a ring; each  $R_{521}$  is independently H,  $C_{1-10}$  alkyl, or  $C_{2-10}$  alkenyl;  $R_{621}$  is a bond, alkyl, or alkenyl, which may be interrupted by one or more  $-O-$  groups;

$R_{721}$  is  $C_{1-10}$  alkyl; or  $R_{321}$  and  $R_{721}$  can join together to form a ring;

$v$  is 0 to 4; and

each  $R_{21}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



XXII

wherein: X is  $-\text{CHR}_{522}-$ ,  $-\text{CHR}_{522}\text{-alkyl}-$ , or  $-\text{CHR}_{522}\text{-alkenyl}-$ ;

$R_{122}$  is selected from:

- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}-\text{alkyl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}-\text{alkenyl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}-\text{aryl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}-\text{heteroaryl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}-\text{heterocyclyl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{722};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}-\text{alkyl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}-\text{alkenyl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}-\text{aryl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}-\text{heteroaryl};$
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}-\text{heterocyclyl};$  and
- $-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NH}_2;$

$R_{222}$  is selected from:

- $-\text{hydrogen};$

-alkyl;  
 -alkenyl;  
 -aryl;  
 -heteroaryl;  
 5 -heterocyclyl;  
 -alkyl-Y-alkyl;  
 -alkyl-Y-alkenyl;  
 -alkyl-Y-aryl; and  
 -alkyl or alkenyl substituted by one or more substituents selected  
 10 from:

-OH;  
 -halogen;  
 -N(R<sub>522</sub>)<sub>2</sub>;  
 -CO-N(R<sub>522</sub>)<sub>2</sub>;  
 15 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 20 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

Y is -O- or -S(O)<sub>0-2</sub>;

R<sub>322</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl;

25 each R<sub>422</sub> is independently alkyl or alkenyl, which may be interrupted by  
 one or more -O- groups; or R<sub>322</sub> and R<sub>422</sub> can join together to form a ring;

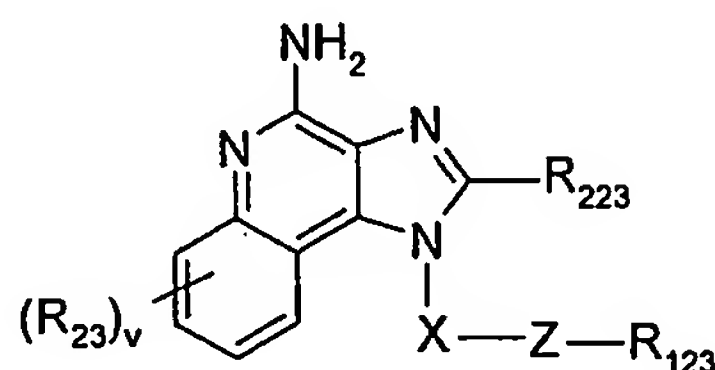
each R<sub>522</sub> is independently H, C<sub>1-10</sub> alkyl, or C<sub>2-10</sub> alkenyl;

R<sub>622</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -  
 O- groups;

30 R<sub>722</sub> is C<sub>1-10</sub> alkyl; or R<sub>322</sub> and R<sub>722</sub> can join together to form a ring;

v is 0 to 4; and

each  $R_{22}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



XXIII

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wherein: X is  $-CHR_{323}-$ ,  $-CHR_{323}$ -alkyl-, or  $-CHR_{323}$ -alkenyl-;

Z is  $-S-$ ,  $-SO-$ , or  $-SO_2-$ ;

$R_{123}$  is selected from:

10

-alkyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkenyl;

15

$-R_{423}$ -aryl;

$-R_{423}$ -heteroaryl; and

$-R_{423}$ -heterocyclyl;

$R_{223}$  is selected from:

-hydrogen;

20

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

25

-alkyl-Y-alkyl;

-alkyl-Y-alkenyl;

-alkyl-Y-aryl; and

-alkyl or alkenyl substituted by one or more substituents selected from:

-OH;  
 -halogen;  
 -N(R<sub>323</sub>)<sub>2</sub>;  
 -CO-N(R<sub>323</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

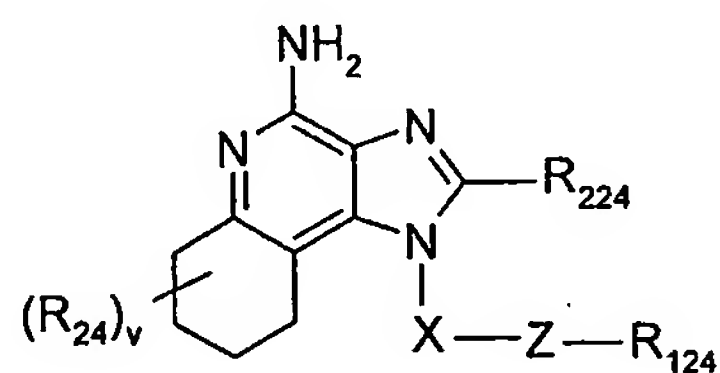
each R<sub>323</sub> is independently H or C<sub>1-10</sub> alkyl;

each R<sub>423</sub> is independently alkyl or alkenyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each R<sub>23</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



XXIV

wherein: X is -CHR<sub>324</sub>-, -CHR<sub>324</sub>-alkyl-, or -CHR<sub>324</sub>-alkenyl-;

Z is -S-, -SO-, or -SO<sub>2</sub>-;

R<sub>124</sub> is selected from:

-alkyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;



-alkenyl;  
-R<sub>424</sub>-aryl;  
-R<sub>424</sub>-heteroaryl; and  
-R<sub>424</sub>-heterocyclyl;

5 R<sub>224</sub> is selected from:

-hydrogen;  
-alkyl;  
-alkenyl;  
-aryl;  
10 -heteroaryl;  
-heterocyclyl;  
-alkyl-Y-alkyl;  
-alkyl-Y-alkenyl;  
-alkyl-Y-aryl; and

15 -alkyl or alkenyl substituted by one or more substituents selected  
from:

-OH;  
-halogen;  
-N(R<sub>324</sub>)<sub>2</sub>;  
20 -CO-N(R<sub>324</sub>)<sub>2</sub>;  
-CO-C<sub>1-10</sub> alkyl;  
-CO-O-C<sub>1-10</sub> alkyl;  
-N<sub>3</sub>;  
-aryl;  
25 -heteroaryl;  
-heterocyclyl;  
-CO-aryl; and  
-CO-heteroaryl;

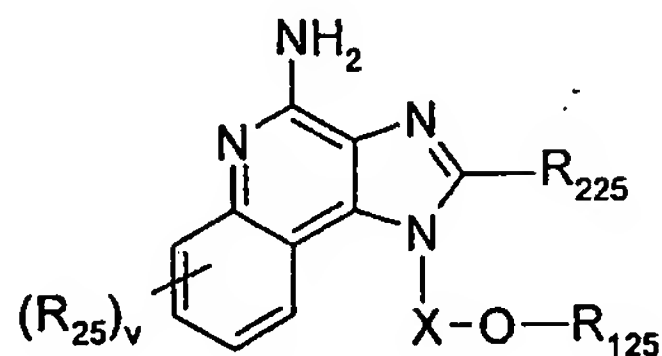
each R<sub>324</sub> is independently H or C<sub>1-10</sub> alkyl;

30 each R<sub>424</sub> is independently alkyl or alkenyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each  $R_{24}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



XXV

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wherein: X is  $-CHR_{525}-$ ,  $-CHR_{525}$ -alkyl-, or  $-CHR_{525}$ -alkenyl-;

$R_{125}$  is selected from:

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- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}$ -alkyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}$ -alkenyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}$ -aryl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}$ -heteroaryl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}-Z-R_{625}$ -heterocyclyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{525}R_{725}$ ;
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}$ -alkyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}$ -alkenyl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}$ -aryl;
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}$ -heteroaryl; and
- $-R_{425}-NR_{825}-CR_{325}-NR_{925}-Z-R_{625}$ -heterocyclyl;

15

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$R_{225}$  is selected from:

25

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from:

-OH;  
-halogen;  
-N(R<sub>525</sub>)<sub>2</sub>;  
-CO-N(R<sub>525</sub>)<sub>2</sub>;  
-CO-C<sub>1-10</sub> alkyl;  
-CO-O-C<sub>1-10</sub> alkyl;  
-N<sub>3</sub>;  
-aryl;  
-heteroaryl;  
-heterocyclyl;  
-CO-aryl; and  
-CO-heteroaryl;

each R<sub>325</sub> is =O or =S;

each R<sub>425</sub> is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups;

each R<sub>525</sub> is independently H or C<sub>1-10</sub> alkyl;

R<sub>625</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R<sub>725</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a hetero atom, or R<sub>725</sub> can join with R<sub>525</sub> to form a ring;

R<sub>825</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>425</sub> and R<sub>825</sub> can join together to form a ring;

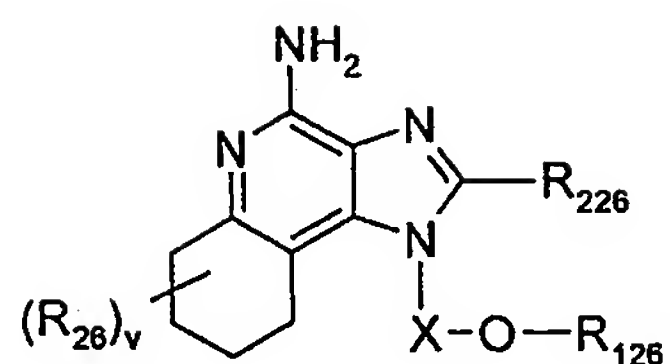
R<sub>925</sub> is C<sub>1-10</sub> alkyl which can join together with R<sub>825</sub> to form a ring;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

Z is a bond, -CO-, or -SO<sub>2</sub>-;

v is 0 to 4; and

each R<sub>25</sub> present is independently selected C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



XXVI

wherein: X is  $-\text{CHR}_{526}-$ ,  $-\text{CHR}_{526}\text{-alkyl}-$ , or  $-\text{CHR}_{526}\text{-alkenyl}-$ ;

5  $\text{R}_{126}$  is selected from:

- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{526}-\text{Z}-\text{R}_{626}\text{-alkyl};$
- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{526}-\text{Z}-\text{R}_{626}\text{-alkenyl};$
- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{526}-\text{Z}-\text{R}_{626}\text{-aryl};$
- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{526}-\text{Z}-\text{R}_{626}\text{-heteroaryl};$
- 10  $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{526}-\text{Z}-\text{R}_{626}\text{-heterocyclyl};$
- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{526}\text{R}_{726};$
- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{926}-\text{Z}-\text{R}_{626}\text{-alkyl};$
- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{926}-\text{Z}-\text{R}_{626}\text{-alkenyl};$
- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{926}-\text{Z}-\text{R}_{626}\text{-aryl};$
- 15  $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{926}-\text{Z}-\text{R}_{626}\text{-heteroaryl};$  and
- $-\text{R}_{426}-\text{NR}_{826}-\text{CR}_{326}-\text{NR}_{926}-\text{Z}-\text{R}_{626}\text{-heterocyclyl};$

$\text{R}_{226}$  is selected from:

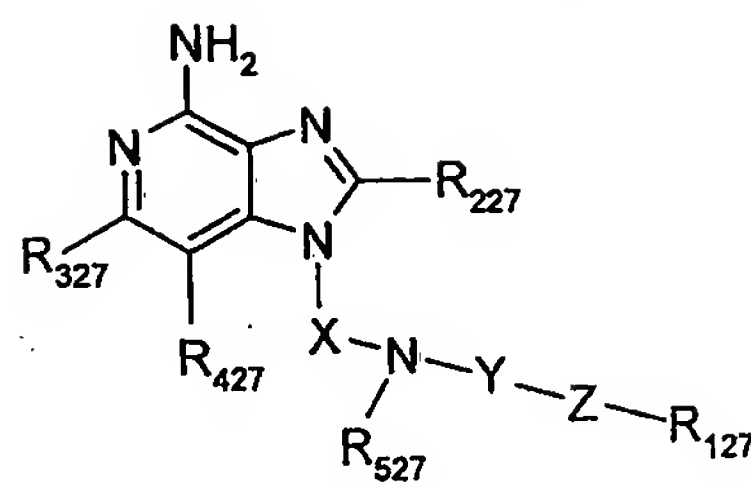
- hydrogen;
- alkyl;
- 20 -alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- 25 -alkyl-Y-alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents selected from:

-OH;

- halogen;
  - N(R<sub>526</sub>)<sub>2</sub>;
  - CO-N(R<sub>526</sub>)<sub>2</sub>;
  - CO-C<sub>1-10</sub> alkyl;
  - 5 -CO-O-C<sub>1-10</sub> alkyl;
  - N<sub>3</sub>;
  - aryl;
  - heteroaryl;
  - heterocyclyl;
  - 10 -CO-aryl; and
  - CO-heteroaryl;
- each R<sub>326</sub> is =O or =S;
- each R<sub>426</sub> is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups;
- 15 each R<sub>526</sub> is independently H or C<sub>1-10</sub> alkyl;
- R<sub>626</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;
- R<sub>726</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a hetero atom, or R<sub>726</sub> can join with R<sub>526</sub> to form a ring;
- 20 R<sub>826</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>426</sub> and R<sub>826</sub> can join together to form a ring;
- R<sub>926</sub> is C<sub>1-10</sub> alkyl which can join together with R<sub>826</sub> to form a ring;
- each Y is independently -O- or -S(O)<sub>0-2</sub>-;
- Z is a bond, -CO-, or -SO<sub>2</sub>-;
- 25 v is 0 to 4; and
- each R<sub>26</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;

and pharmaceutically acceptable salts of any of the foregoing.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-  
 30 *c*]pyridin-4-amines defined by Formula XXVII below:



XXVII

wherein

X is alkylene or alkenylene;

5

Y is  $-\text{CO}-$  or  $-\text{CS}-$ ;

Z is a bond,  $-\text{O}-$ , or  $-\text{S}-$ ;

$\text{R}_{127}$  is aryl, heteroaryl, heterocyclyl, alkyl or

alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

10

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

15

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

20

-O-(alkyl)<sub>0-1</sub>-aryl;

-O-(alkyl)<sub>0-1</sub>-(substituted aryl);

-O-(alkyl)<sub>0-1</sub>-heteroaryl;

-O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);

-O-(alkyl)<sub>0-1</sub>-heterocyclyl;

25

-O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);

-COOH;

-CO-O-alkyl;

-CO-alkyl;

- S(O)<sub>0-2</sub>-alkyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
 5 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);  
 -(alkyl)<sub>0-1</sub>-N(R<sub>627</sub>)<sub>2</sub>;  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-O-alkyl;  
 10 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-alkyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-aryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-(substituted aryl);  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-heteroaryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-(substituted heteroaryl);  
 15 -N<sub>3</sub>;  
 -halogen;  
 -haloalkyl;  
 -haloalkoxy;  
 -CO-haloalkyl;  
 20 -CO-haloalkoxy;  
 -NO<sub>2</sub>;  
 -CN;  
 -OH;  
 -SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;
- 25 R<sub>227</sub> is selected from:  
 -hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 30 -substituted aryl;  
 -heteroaryl;  
 -substituted heteroaryl;

- alkyl-O-alkyl;
- alkyl-S-alkyl;
- alkyl-O-aryl;
- alkyl-S-aryl;
- 5 -alkyl-O- alkenyl;
- alkyl-S- alkenyl; and
- alkyl or alkenyl substituted by one or more substituents selected from:
- OH;
- 10 -halogen;
- N(R<sub>627</sub>)<sub>2</sub>;
- CO-N(R<sub>627</sub>)<sub>2</sub>;
- CS-N(R<sub>627</sub>)<sub>2</sub>;
- SO<sub>2</sub>-N(R<sub>627</sub>)<sub>2</sub>;
- 15 -NR<sub>627</sub>-CO-C<sub>1-10</sub> alkyl;
- NR<sub>627</sub>-CS-C<sub>1-10</sub> alkyl;
- NR<sub>627</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;
- CO-C<sub>1-10</sub> alkyl;
- CO-O-C<sub>1-10</sub> alkyl;
- 20 -N<sub>3</sub>;
- aryl;
- substituted aryl;
- heteroaryl;
- substituted heteroaryl;
- 25 -heterocyclyl;
- substituted heterocyclyl;
- CO-aryl;
- CO-(substituted aryl);
- CO-heteroaryl; and
- 30 -CO-(substituted heteroaryl);

R<sub>327</sub> and R<sub>427</sub> are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

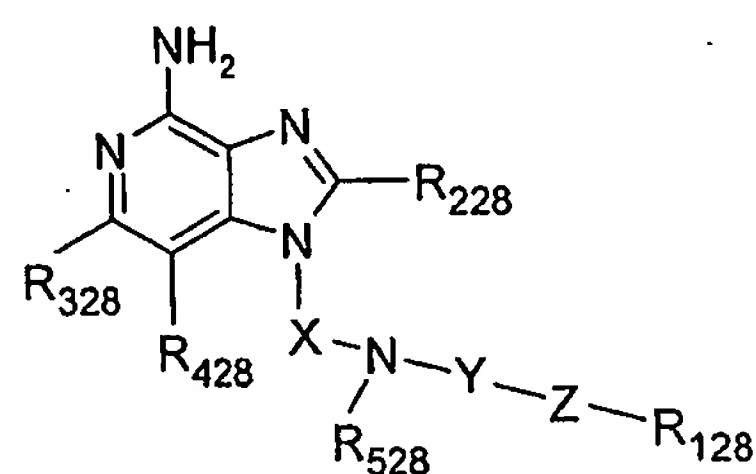


$R_{527}$  is H or  $C_{1-10}$  alkyl, or  $R_{527}$  can join with X to form a ring that contains one or two heteroatoms; or when  $R_{127}$  is alkyl,  $R_{527}$  and  $R_{127}$  can join to form a ring;

each  $R_{627}$  is independently H or  $C_{1-10}$ alkyl;

5 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXVIII below:



XXVIII

10

wherein

X is alkylene or alkenylene;

Y is  $-SO_2-$ ;

Z is a bond or  $-NR_{628}-$ ;

$R_{128}$  is aryl, heteroaryl, heterocyclyl, alkyl or

15

alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

-alkyl;

-alkenyl;

-aryl;

20

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

25

-substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)<sub>0-1</sub>-aryl;

-O-(alkyl)<sub>0-1</sub>-(substituted aryl);

- 5
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
  - O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
  - O-(alkyl)<sub>0-1</sub>-heterocyclyl;
  - O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);
  - COOH;
  - CO-O-alkyl;
  - CO-alkyl;
  - S(O)<sub>0-2</sub>-alkyl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;

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  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);

15

  - (alkyl)<sub>0-1</sub>-N(R<sub>628</sub>)<sub>2</sub>;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-O-alkyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-alkyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-aryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-(substituted aryl);

20

  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-heteroaryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-(substituted heteroaryl);
  - N<sub>3</sub>;
  - halogen;
  - haloalkyl;

25

  - haloalkoxy;
  - CO-haloalkyl;
  - CO-haloalkoxy;
  - NO<sub>2</sub>;
  - CN;

30

  - OH;
  - SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R<sub>228</sub> is selected from:

- 5                    -hydrogen;  
                  -alkyl;  
                  -alkenyl;  
                  -aryl;  
                  -substituted aryl;  
                  -heteroaryl;  
                  -substituted heteroaryl;  
                  -alkyl-O-alkyl;  
                  -alkyl-S-alkyl;  
10                   -alkyl-O-aryl;  
                  -alkyl-S-aryl;  
                  -alkyl-O- alkenyl;  
                  -alkyl-S- alkenyl; and  
                  -alkyl or alkenyl substituted by one or more substituents selected  
15                   from:  
                  -OH;  
                  -halogen;  
                  -N(R<sub>628</sub>)<sub>2</sub>;  
                  -CO-N(R<sub>628</sub>)<sub>2</sub>;  
20                   -CS-N(R<sub>628</sub>)<sub>2</sub>;  
                  -SO<sub>2</sub>-N(R<sub>628</sub>)<sub>2</sub>;  
                  -NR<sub>628</sub>-CO-C<sub>1-10</sub> alkyl;  
                  -NR<sub>628</sub>-CS-C<sub>1-10</sub> alkyl;  
                  -NR<sub>628</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;  
25                   -CO-C<sub>1-10</sub> alkyl;  
                  -CO-O-C<sub>1-10</sub> alkyl;  
                  -N<sub>3</sub>;  
                  -aryl;  
                  -substituted aryl;  
30                   -heteroaryl;  
                  -substituted heteroaryl;  
                  -heterocyclyl;

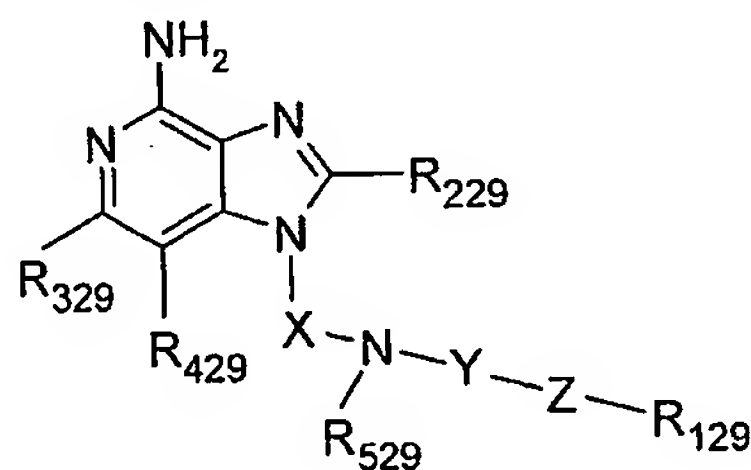
-substituted heterocyclyl;  
 -CO-aryl;  
 -CO-(substituted aryl);  
 -CO-heteroaryl; and  
 -CO-(substituted heteroaryl);

$R_{328}$  and  $R_{428}$  are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

$R_{528}$  is H or  $C_{1-10}$  alkyl, or  $R_{528}$  can join with X to form a ring; or when  $R_{128}$  is alkyl,  $R_{528}$  and  $R_{128}$  can join to form a ring;

each  $R_{628}$  is independently H or  $C_{1-10}$ alkyl;  
 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXIX below:



XXIX

wherein

X is alkylene or alkenylene;

Y is -CO- or -CS;

Z is -NR<sub>629</sub>-, -NR<sub>629</sub>-CO-, -NR<sub>629</sub>-SO<sub>2</sub>-, or -NR<sub>729</sub>-;

$R_{129}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

-alkyl;  
 -alkenyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -substituted cycloalkyl;

- substituted aryl;  
-substituted heteroaryl;  
-substituted heterocyclyl;  
-O-alkyl;  
5 -O-(alkyl)<sub>0-1</sub>-aryl;  
-O-(alkyl)<sub>0-1</sub>-(substituted aryl);  
-O-(alkyl)<sub>0-1</sub>-heteroaryl;  
-O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
-O-(alkyl)<sub>0-1</sub>-heterocyclyl;  
10 -O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);  
-COOH;  
-CO-O-alkyl;  
-CO-alkyl;  
-S(O)<sub>0-2</sub>-alkyl;  
15 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
-S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
20 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);  
-(alkyl)<sub>0-1</sub>-N(R<sub>629</sub>)<sub>2</sub>;  
-(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-O-alkyl;  
-(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-alkyl;  
-(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-aryl;  
25 -(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-(substituted aryl);  
-(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-heteroaryl;  
-(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-(substituted heteroaryl);  
-P(O)(O-alkyl)<sub>2</sub>;  
-N<sub>3</sub>;  
30 -halogen;  
-haloalkyl;  
-haloalkoxy;

-CO-haloalkyl;  
-CO-haloalkoxy;  
-NO<sub>2</sub>;  
-CN;  
-OH;  
-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R<sub>229</sub> is selected from:

-hydrogen;  
-alkyl;  
-alkenyl;  
-aryl;  
-substituted aryl;  
-heteroaryl;  
-substituted heteroaryl;  
-alkyl-O-alkyl;  
-alkyl-S-alkyl;  
-alkyl-O-aryl;  
-alkyl-S-aryl;  
-alkyl-O- alkenyl;  
-alkyl-S- alkenyl; and  
-alkyl or alkenyl substituted by one or more substituents selected  
from:

-OH;  
-halogen;  
-N(R<sub>629</sub>)<sub>2</sub>;  
-CO-N(R<sub>629</sub>)<sub>2</sub>;  
-CS-N(R<sub>629</sub>)<sub>2</sub>;  
-SO<sub>2</sub>-N(R<sub>629</sub>)<sub>2</sub>;  
-NR<sub>629</sub>-CO-C<sub>1-10</sub> alkyl;  
-NR<sub>629</sub>-CS-C<sub>1-10</sub> alkyl;  
-NR<sub>629</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;  
-CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -substituted aryl;  
 -heteroaryl;  
 -substituted heteroaryl;  
 -heterocyclyl;  
 -substituted heterocyclyl;  
 -CO-aryl;  
 -CO-(substituted aryl);  
 -CO-heteroaryl; and  
 -CO-(substituted heteroaryl);

R<sub>329</sub> and R<sub>429</sub> are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

R<sub>529</sub> is H or C<sub>1-10</sub> alkyl, or R<sub>529</sub> can join with X to form a ring that contains one or two heteroatoms;

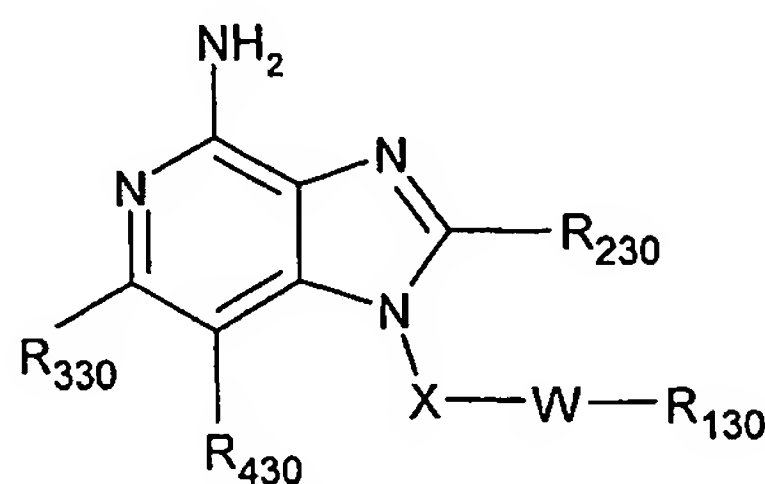
each R<sub>629</sub> is independently H or C<sub>1-10</sub>alkyl;

R<sub>729</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a heteroatom; or when

R<sub>129</sub> is alkyl, R<sub>729</sub> and R<sub>129</sub> can join to form a ring;

and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1-position ether or thioether substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXX below:



XXX

wherein:

X is -CH(R<sub>530</sub>)-, -CH(R<sub>530</sub>)-alkylene-, -CH(R<sub>530</sub>)-alkenylene-,  
or CH(R<sub>530</sub>)-alkylene-Y-alkylene-;

Y is -O-, or -S(O)<sub>0-2</sub>-;

-W-R<sub>130</sub> is selected from -O-R<sub>130-1-5</sub> and -S(O)<sub>0-2</sub>-R<sub>130-6</sub>;

5 R<sub>130-1-5</sub> is selected from

- R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-alkyl;
- R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-alkenyl;
- R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-aryl;
- R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-heteroaryl;
- 10 -R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-heterocyclyl;
- R<sub>630</sub>-C(R<sub>730</sub>)-Z-H;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-alkyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-alkenyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-aryl;
- 15 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-heteroaryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-heterocyclyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>1030</sub>;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-alkyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-alkenyl;
- 20 -R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-aryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-heteroaryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-heterocyclyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>1030</sub>;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-alkyl;
- 25 -R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-alkenyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-aryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-heteroaryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-heterocyclyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-NH<sub>2</sub>;
- 30 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-alkyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-alkenyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-aryl;



-R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-heteroaryl;  
 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-heterocyclyl;  
 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)<sub>2</sub>;

-R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N  $\bigcirc$  A ;

5 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-alkyl;  
 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-alkenyl;  
 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-aryl;  
 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-heteroaryl;  
 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-heterocyclyl;  
 10 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)H;  
 -alkenyl;  
 -aryl;  
 -R<sub>630</sub>-aryl;  
 -heteroaryl;  
 15 -heterocyclyl;  
 -R<sub>630</sub>-heteroaryl; and  
 -R<sub>630</sub>-heterocyclyl;

Z is -N(R<sub>530</sub>)-, -O-, or -S-;

Q is a bond, -CO-, or -SO<sub>2</sub>-;

20 A represents the atoms necessary to provide a 5- or 6-membered heterocyclic or heteroaromatic ring that contains up to three heteroatoms;

R<sub>130-6</sub> is selected from:

-alkyl;  
 -aryl;  
 25 -heteroaryl;  
 -heterocyclyl;  
 -alkenyl;  
 -R<sub>630</sub>-aryl;  
 -R<sub>630</sub>-heteroaryl; and  
 30 -R<sub>630</sub>-heterocyclyl;

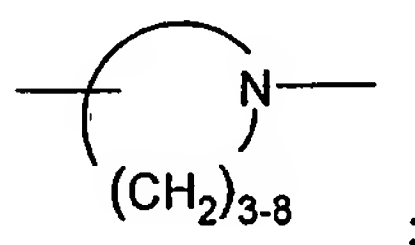
each R<sub>530</sub> is independently hydrogen, C<sub>1-10</sub> alkyl, or C<sub>2-10</sub> alkenyl;

R<sub>630</sub> is alkylene, alkenylene, or alkynylene, which may be interrupted by one or more -O- groups;

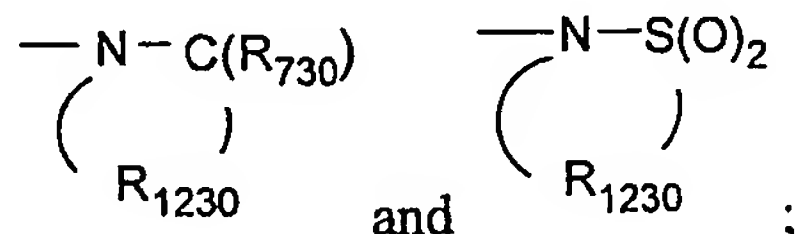
R<sub>730</sub> is =O or =S;

R<sub>830</sub> is a bond, alkylene, alkenylene, or alkynylene, which may be interrupted by  
5 one or more -O- groups;

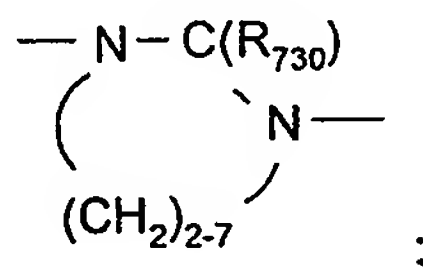
R<sub>930</sub> is hydrogen, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>930</sub> can join together with any carbon atom of R<sub>630</sub> to form a ring of the formula



R<sub>1030</sub> is hydrogen or C<sub>1-10</sub> alkyl; or R<sub>930</sub> and R<sub>1030</sub> can join together to form a ring  
10 selected from



R<sub>1130</sub> is C<sub>1-10</sub> alkyl; or R<sub>930</sub> and R<sub>1130</sub> can join together to form a ring having the structure



15 R<sub>1230</sub> is C<sub>2-7</sub> alkylene which is straight chain or branched, wherein the branching does not prevent formation of the ring; and

R<sub>230</sub>, R<sub>330</sub> and R<sub>430</sub> are independently selected from hydrogen and non-interfering substituents;

and pharmaceutically acceptable salts thereof.

20 Illustrative non-interfering R<sub>230</sub> substituents include:

-alkyl;

**-alkenyl;**

-aryl;

**-heteroaryl;**

25 -heterocyclyl;

-alkylene-Y-alkyl;

-alkylene-Y- alkenyl;

-alkylene-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

5 -halogen;

-N(R<sub>530</sub>)<sub>2</sub>;

-C(O)-C<sub>1-10</sub> alkyl;

-C(O)-O-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

10 -aryl;

-heteroaryl;

-heterocyclyl;

-C(O)-aryl; and

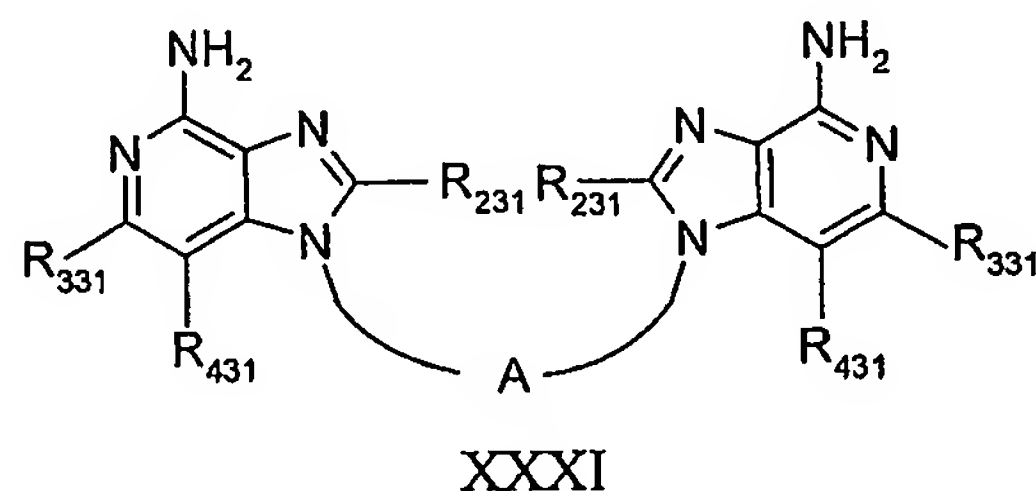
-C(O)-heteroaryl.

15 Illustrative non-interfering R<sub>330</sub> and R<sub>430</sub> substituents include:

C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>1-10</sub> alkoxy, C<sub>1-10</sub> alkylthio, amino, alkylamino, dialkylamino, halogen, and nitro.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo dimers of the formula (XXXI):

20



wherein:

A is a divalent linking group selected from the group consisting of:

25 straight or branched chain C<sub>4-20</sub> alkylene;

straight or branched chain C<sub>4-20</sub> alkenylene;

straight or branched chain C<sub>4-20</sub> alkynylene; and

-Z-Y-W-Y-Z-;

each Z is independently selected from the group consisting of:

straight or branched chain C<sub>2-20</sub> alkylene;  
 straight or branched chain C<sub>4-20</sub> alkenylene; and  
 straight or branched chain C<sub>4-20</sub> alkynylene;  
 any of which may be optionally interrupted by -O-, -N(R<sub>531</sub>)-, or

5 -S(O)<sub>2</sub>-;

each Y is independently selected from the group consisting of:

a bond;

-N(R<sub>531</sub>)C(O)-;

-C(O)N(R<sub>531</sub>)-;

10 -N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)-;

-N(R<sub>531</sub>)S(O)<sub>2</sub>-;

-S(O)<sub>2</sub>N(R<sub>531</sub>)-;

-OC(O)O-;

-OC(O)-;

15 -C(O)O-;

-N(R<sub>531</sub>)C(O)O-; and

-OC(O)N(R<sub>531</sub>)-;

W is selected from the group consisting of:

straight or branched chain C<sub>2-20</sub> alkylene;

20 straight or branched chain C<sub>2-20</sub> alkenylene;

straight or branched chain C<sub>4-20</sub> alkynylene;

straight or branched chain perfluoro C<sub>2-20</sub> alkylene;

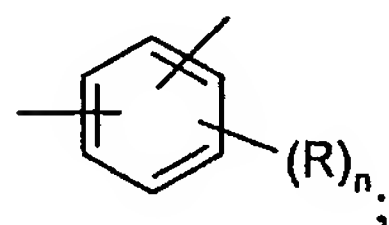
C<sub>1-4</sub> alkylene-O-C<sub>1-4</sub> alkylene;

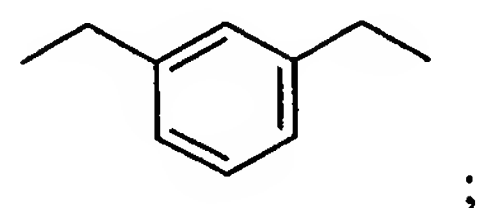
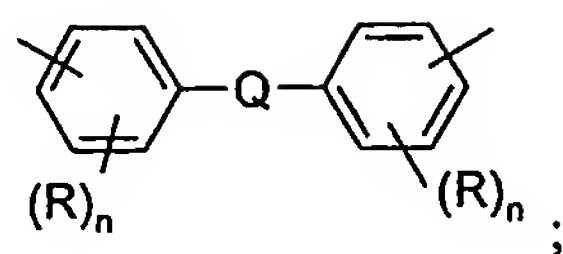
-C(O)-;

25 -S(O)<sub>2</sub>-;

-OC(O)O-;

-N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)-;





1,5-naphthylene;

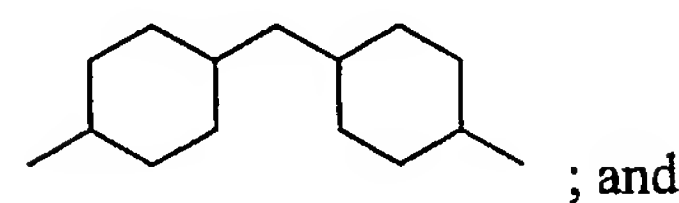
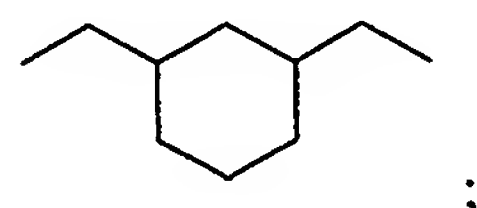
2,6-pyridinylene;

5      1,2-cyclohexylene;

1,3-cyclohexylene;

1,4-cyclohexylene;

trans-1,4-cyclohexylene;



trans-5-norbornen-2,3-diyl;

wherein n is 0 - 4; each R is independently selected from the group consisting of C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, and halogen; and Q is selected from the group consisting of a bond, -CH<sub>2</sub>-, and -O-;

15      R<sub>231</sub> is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

20      -substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-alkyl-X-alkyl;

-alkyl-X-aryl;

25      -alkyl-X- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

- OH;
- halogen;
- 5        -N(R<sub>631</sub>)<sub>2</sub>;
- C(O)-N(R<sub>631</sub>)<sub>2</sub>;
- C(S)-N(R<sub>631</sub>)<sub>2</sub>;
- S(O)<sub>2</sub>-N(R<sub>631</sub>)<sub>2</sub>;
- N(R<sub>631</sub>)-C(O)-C<sub>1-10</sub> alkyl;
- 10       -N(R<sub>631</sub>)-C(S)-C<sub>1-10</sub> alkyl;
- N(R<sub>631</sub>)-S(O)<sub>2</sub>-C<sub>1-10</sub> alkyl;
- C(O)-C<sub>1-10</sub> alkyl;
- C(O)-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- 15       -aryl;
- substituted aryl;
- heteroaryl;
- substituted heteroaryl;
- heterocyclyl;
- 20       -substituted heterocyclyl;
- C(O)-aryl;
- C(O)-(substituted aryl);
- C(O)-heteroaryl; and
- C(O)-(substituted heteroaryl);

25       R<sub>331</sub> and R<sub>431</sub> are each independently selected from the group consisting of:

- hydrogen;
- halogen;
- alkyl;
- alkenyl;
- 30       -X-alkyl; and
- N(R<sub>631</sub>)<sub>2</sub>;

or when taken together,  $R_{331}$  and  $R_{431}$  form a fused aryl or heteroaryl ring that is unsubstituted or substituted by one or more substituents selected from the group consisting of:

- halogen;
- alkyl;
- alkenyl;
- X-alkyl; and
- $N(R_{631})_2$ ;

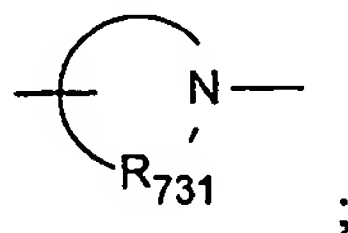
or when taken together,  $R_{331}$  and  $R_{431}$  form a fused 5 to 7 membered saturated ring, containing 0 to 2 heteroatoms and unsubstituted or substituted by one or more substituents selected from the group consisting of:

- halogen;
- alkyl;
- alkenyl;
- X-alkyl; and
- $N(R_{631})_2$ ;

each  $R_{531}$  is independently selected from the group consisting of:

- hydrogen;
- $C_{1-6}$  alkyl;
- $C_{3-7}$  cycloalkyl; and
- benzyl; or

when Y is  $-N(R_{531})C(O)-$ ,  $-C(O)N(R_{531})-$ ,  $-N(R_{531})C(O)N(R_{531})-$ ,  $-N(R_{531})S(O)_2-$ ,  $-S(O)_2N(R_{531})-$ ,  $-N(R_{531})C(O)O-$ , or  $-OC(O)N(R_{531})-$  and the nitrogen of the  $N(R_{531})$  group is bonded to Z, then  $R_{531}$  can join with Z to form a ring having the structure



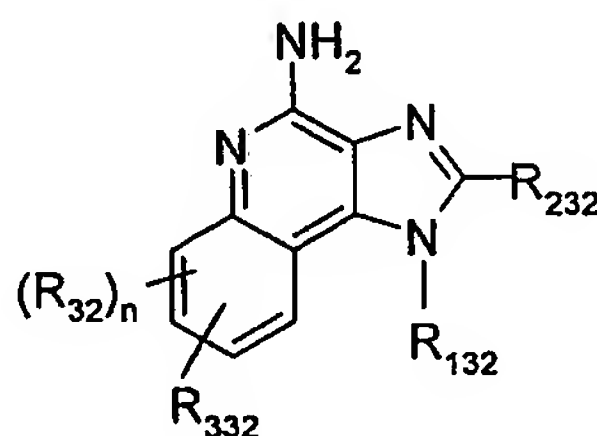
each  $R_{631}$  is independently hydrogen or  $C_{1-10}$  alkyl;

$R_{731}$  is  $C_{3-8}$  alkylene; and

X is -O- or -S-;

with the proviso that if W is -C(O)-, -S(O)<sub>2</sub>-, -OC(O)O-, or -N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)- then each Y is a bond; and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 6-, 7-, 8-, or 9-position aryl or heteroaryl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amines of the following Formula (XXXII):



XXXII

wherein:

R<sub>32</sub> is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

n is 0 or 1;

R<sub>132</sub> and R<sub>232</sub> are independently selected from the group consisting of hydrogen and non-interfering substituents;

R<sub>332</sub> is selected from the group consisting of:

-Z-Ar,

-Z-Ar'-Y-R<sub>432</sub>,

-Z-Ar'-X-Y-R<sub>432</sub>,

-Z-Ar'-R<sub>532</sub>, and

-Z-Ar'-X-R<sub>532</sub>;

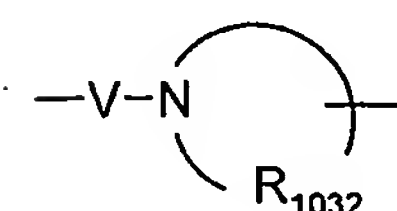
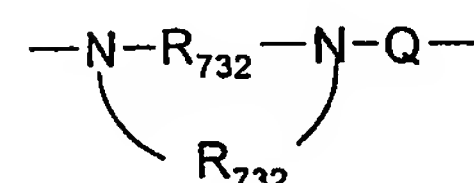
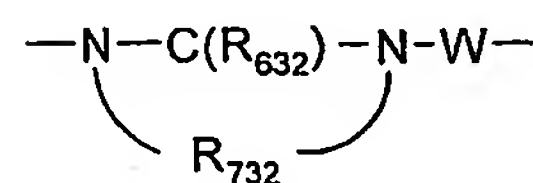
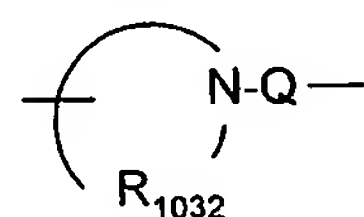
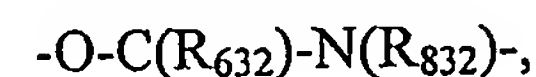
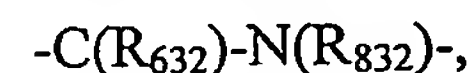
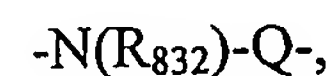
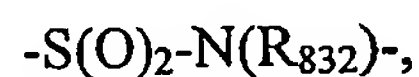
Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;



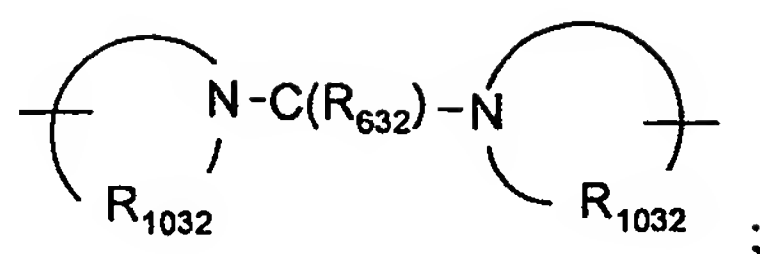
Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:



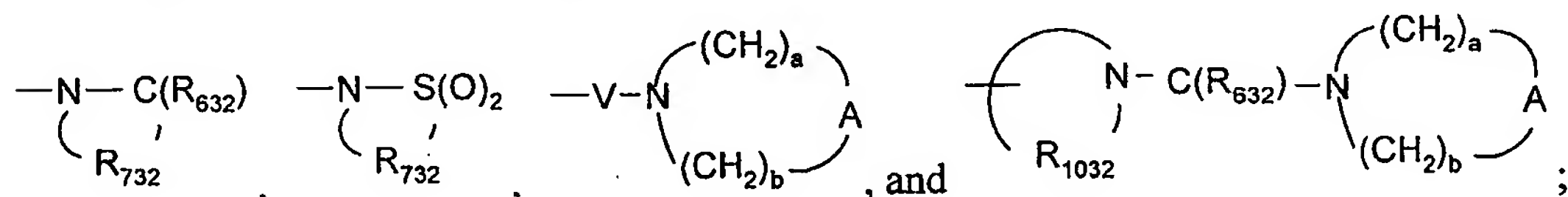
, and



Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene;

R<sub>432</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R<sub>532</sub> is selected from the group consisting of:



each R<sub>632</sub> is independently selected from the group consisting of =O and =S;

each R<sub>732</sub> is independently C<sub>2-7</sub> alkylene;

each R<sub>832</sub> is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R<sub>932</sub> is selected from the group consisting of hydrogen and alkyl;

each R<sub>1032</sub> is independently C<sub>3-8</sub> alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>432</sub>)-;

Q is selected from the group consisting of a bond, -C(R<sub>632</sub>)-, -C(R<sub>632</sub>)-C(R<sub>632</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>632</sub>)-N(R<sub>832</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>832</sub>)-, -C(R<sub>632</sub>)-O-, and -C(R<sub>632</sub>)-N(OR<sub>932</sub>)-;

V is selected from the group consisting of -C(R<sub>632</sub>)-, -O-C(R<sub>632</sub>)-,

-N(R<sub>832</sub>)-C(R<sub>632</sub>)-, and -S(O)<sub>2</sub>-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

a and b are independently integers from 1 to 6 with the proviso that  $a + b$  is  $\leq 7$ ;

and pharmaceutically acceptable salts thereof.

5 Illustrative non-interfering R<sub>132</sub> substituents include:

-R<sub>432</sub>,

-X-R<sub>432</sub>,

-X-Y-R<sub>432</sub>,

-X-Y-X-Y-R<sub>432</sub>, and

10 -X-R<sub>532</sub>;

wherein:

each X is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

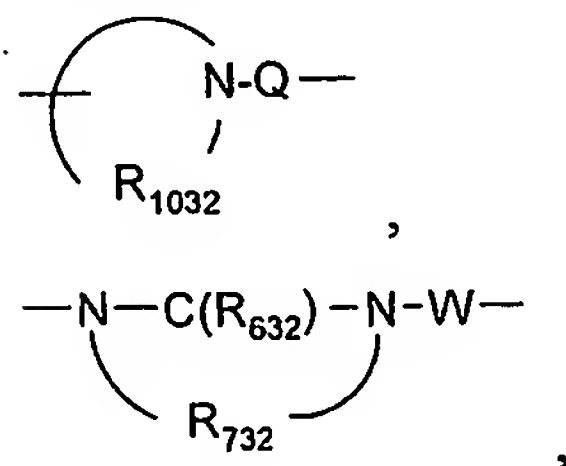
$$-S(O)_{0-2}^-,$$
$$-\text{S}(\text{O})_2-\text{N}(\text{R}_{832})-$$

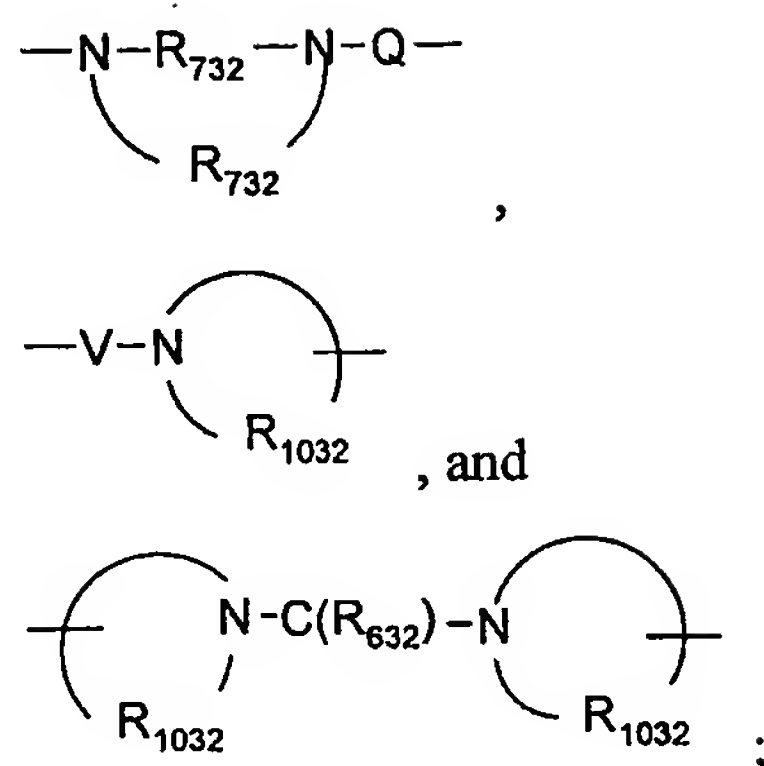
20  $-\text{C}(\text{R}_{632})-$ ,

$$-\text{C}(\text{R}_{632})-\text{O}-,$$
$$-\text{O}-\text{C}(\text{R}_{632})-$$
$$-O-C(O)-O-$$

-N(R<sub>832</sub>)-Q-,

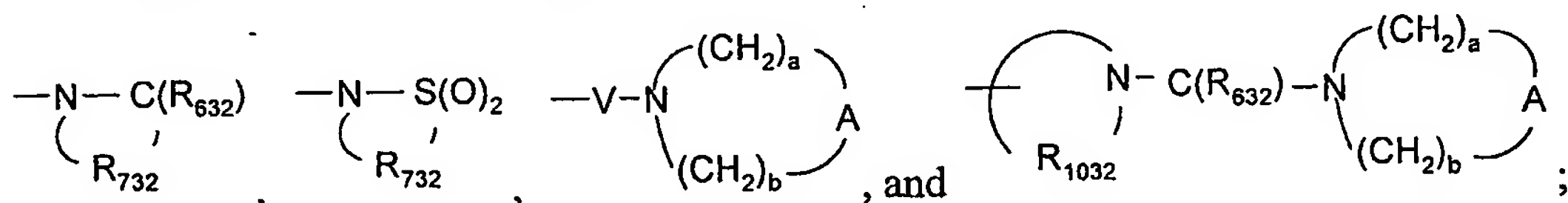
25  $-\text{C}(\text{R}_{632})-\text{N}(\text{R}_{832})-$ ,

$$-\text{O}-\text{C}(\text{R}_{632})-\text{N}(\text{R}_{832})-$$
$$-\text{C}(\text{R}_{632})-\text{N}(\text{OR}_{932})-$$




$R_{432}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl,  
 5 aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,  
 heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,  
 alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,  
 heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups  
 can be unsubstituted or substituted by one or more substituents independently selected  
 10 from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen,  
 nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,  
 heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,  
 (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,  
 oxo;

15  $R_{532}$  is selected from the group consisting of:



each  $R_{632}$  is independently selected from the group consisting of =O and =S;

each  $R_{732}$  is independently  $C_{2-7}$  alkylene;

each  $R_{832}$  is independently selected from the group consisting of hydrogen, alkyl,  
 20 alkoxyalkylenyl, and arylalkylenyl;

each  $R_{932}$  is independently selected from the group consisting of hydrogen and  
 alkyl;

each  $R_{1032}$  is independently  $C_{3-8}$  alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -  
 25 N( $R_{432}$ )-;

each Q is independently selected from the group consisting of a bond,  
 $-C(R_{632})-$ ,  $-C(R_{632})-C(R_{632})-$ ,  $-S(O)_2-$ ,  $-C(R_{632})-N(R_{832})-W-$ ,  $-S(O)_2-N(R_{832})-$ ,  
 $-C(R_{632})-O-$ , and  $-C(R_{632})-N(OR_{932})-$ ;

each V is independently selected from the group consisting of  $-C(R_{632})-$ ,  
 5  $-O-C(R_{632})-$ ,  $-N(R_{832})-C(R_{632})-$ , and  $-S(O)_2-$ ;

each W is independently selected from the group consisting of a bond,  
 $-C(O)-$ , and  $-S(O)_2-$ ; and

a and b are independently integers from 1 to 6 with the proviso that  $a + b$  is  $\leq 7$ ;

Illustrative non-interfering  $R_{232}$  substituents include:

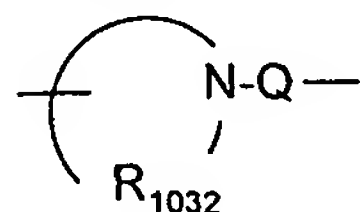
10  $-R_{432}$ ,  
 $-X-R_{432}$ ,  
 $-X-Y-R_{432}$ , and  
 $-X-R_{532}$ ;

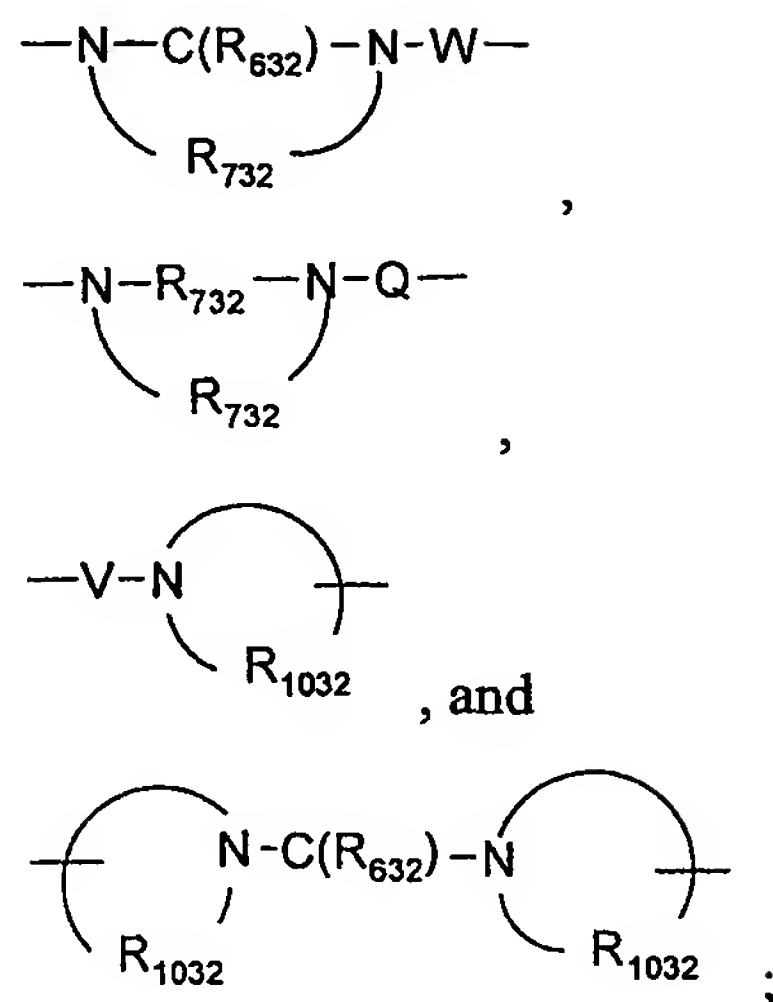
wherein:

15 X is selected from the group consisting of alkylene, alkenylene, alkynylene,  
 arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and  
 alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene,  
 or heterocyclylene, and optionally interrupted by one or more  $-O-$  groups;

Y is selected from the group consisting of:

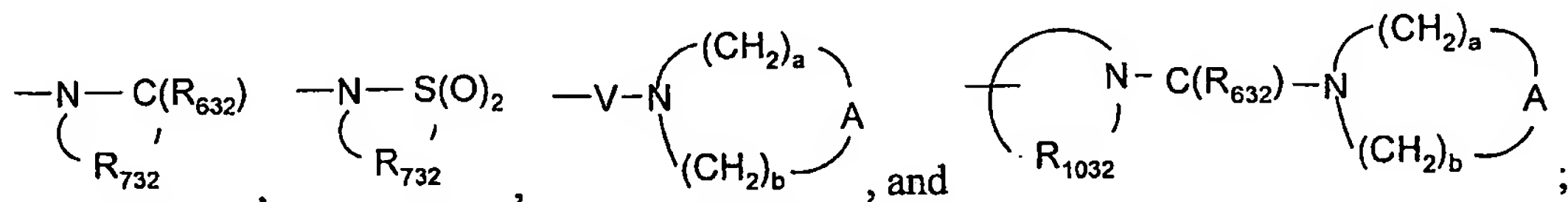
20  $-S(O)_{0-2}-$ ,  
 $-S(O)_2-N(R_{832})-$ ,  
 $-C(R_{632})-$ ,  
 $-C(R_{632})-O-$ ,  
 $-O-C(R_{632})-$ ,  
 25  $-O-C(O)-O-$ ,  
 $-N(R_{832})-Q-$ ,  
 $-C(R_{632})-N(R_{832})-$ ,  
 $-O-C(R_{632})-N(R_{832})-$ ,  
 $-C(R_{632})-N(OR_{932})-$ ,





5 R<sub>432</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups  
10 can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,  
15 oxo;

$R_{532}$  is selected from the group consisting of:



each  $R_{632}$  is independently selected from the group consisting of =O and =S;

each R<sub>732</sub> is independently C<sub>2-7</sub> alkylene;

20            each R<sub>832</sub> is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R<sub>932</sub> is selected from the group consisting of hydrogen and alkyl;

each R<sub>1032</sub> is independently C<sub>3-8</sub> alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>432</sub>)-;

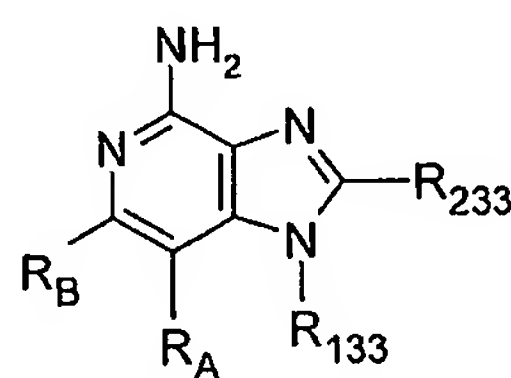
Q is selected from the group consisting of a bond, -C(R<sub>632</sub>)-, -C(R<sub>632</sub>)-C(R<sub>632</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>632</sub>)-N(R<sub>832</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>832</sub>)-, -C(R<sub>632</sub>)-O-, and -C(R<sub>632</sub>)-N(OR<sub>932</sub>)-;

V is selected from the group consisting of -C(R<sub>632</sub>)-, -O-C(R<sub>632</sub>)-, -N(R<sub>832</sub>)-C(R<sub>632</sub>)-, and -S(O)<sub>2</sub>-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

In some embodiments the IRM can be chosen from amide substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amines, tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amines, 1*H*-imidazo[4,5-*c*]pyridin-4-amines, 1*H*-imidazo[4,5-*c*]naphthyridin-4-amines, or tetrahydro-1*H*-imidazo[4,5-*c*]naphthyridin-4-amines of the following Formula XXXIII.

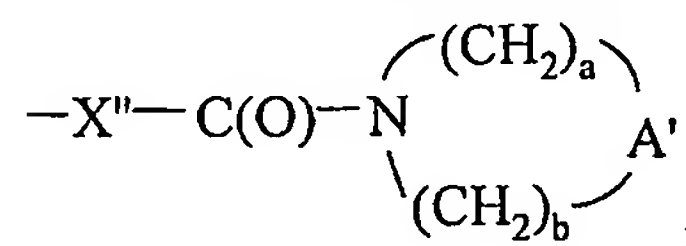


XXXIII

wherein:

R<sub>133</sub> is selected from the group consisting of:

-X'-C(O)-N(R<sub>133'</sub>)(R<sub>133''</sub>) and



X' is selected from the group consisting of -CH(R<sub>933</sub>)-, -CH(R<sub>933</sub>)-alkylene-, and -CH(R<sub>933</sub>)-alkenylene-;

X'' is selected from the group consisting of -CH(R<sub>933</sub>)-, -CH(R<sub>933</sub>)-alkylene-, and -CH(R<sub>933</sub>)-alkenylene-; wherein the alkylene and alkenylene are optionally interrupted with one or more -O- groups;

R<sub>133'</sub> and R<sub>133''</sub> are independently selected from the group consisting of:

hydrogen,  
alkyl,  
alkenyl,  
5 aryl,  
arylalkylenyl,  
heteroaryl,  
heteroarylalkylenyl,  
heterocyclyl,  
10 heterocyclylalkylenyl, and  
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,  
heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents  
selected from the group consisting of:

hydroxy,  
15 alkyl,  
haloalkyl,  
hydroxyalkyl,  
alkoxy,  
haloalkoxy,  
20 halogen,  
cyano,  
nitro,  
amino,  
alkylamino,  
25 dialkylamino,  
arylsulfonyl, and  
alkylsulfonyl;

A' is selected from the group consisting of -O-, -C(O)-, -CH<sub>2</sub>-, -S(O)<sub>0-2</sub>-, and  
-N(Q-R<sub>433</sub>)-;

30 a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R<sub>A</sub> and R<sub>B</sub> are independently selected from the group consisting of:

hydrogen,



halogen,  
alkyl,  
alkenyl,  
alkoxy,  
alkylthio, and  
-N(R<sub>933</sub>)<sub>2</sub>;

or R<sub>A</sub> and R<sub>B</sub> taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R<sub>a</sub> groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R<sub>c</sub> groups;

or R<sub>A</sub> and R<sub>B</sub> taken together form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S, wherein the heteroaryl ring is unsubstituted or substituted by one or more R<sub>b</sub> groups, and the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R<sub>c</sub> groups;

each R<sub>a</sub> is independently selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, and -N(R<sub>933</sub>)<sub>2</sub>;

each R<sub>b</sub> is independently selected from the group consisting of halogen, hydroxy, alkyl, haloalkyl, alkoxy, and -N(R<sub>933</sub>)<sub>2</sub>;

each R<sub>c</sub> is independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and -N(R<sub>933</sub>)<sub>2</sub>;

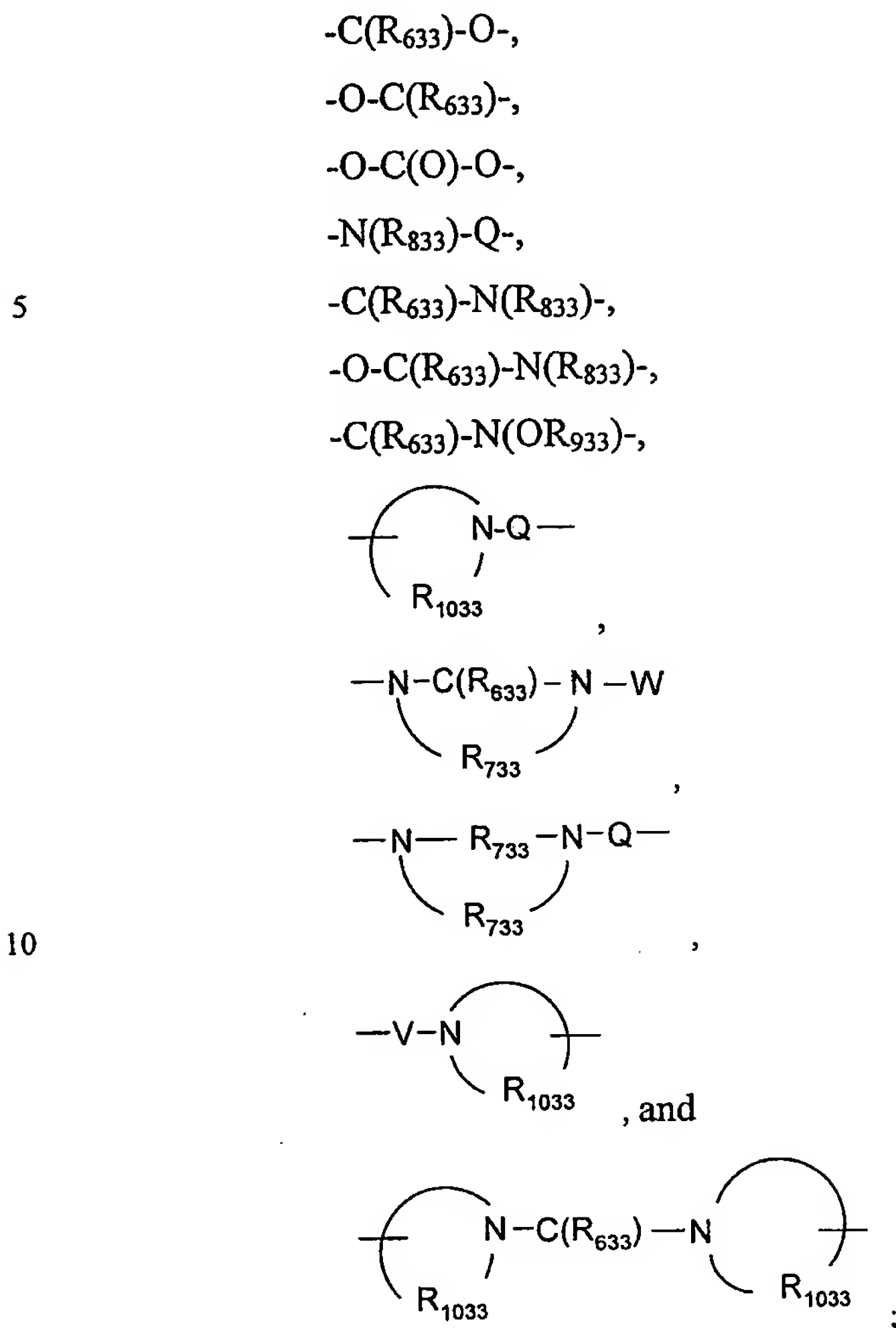
R<sub>233</sub> is selected from the group consisting of:

-R<sub>433</sub>,  
-X-R<sub>433</sub>,  
-X-Y-R<sub>433</sub>, and  
-X-R<sub>533</sub>;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups are optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

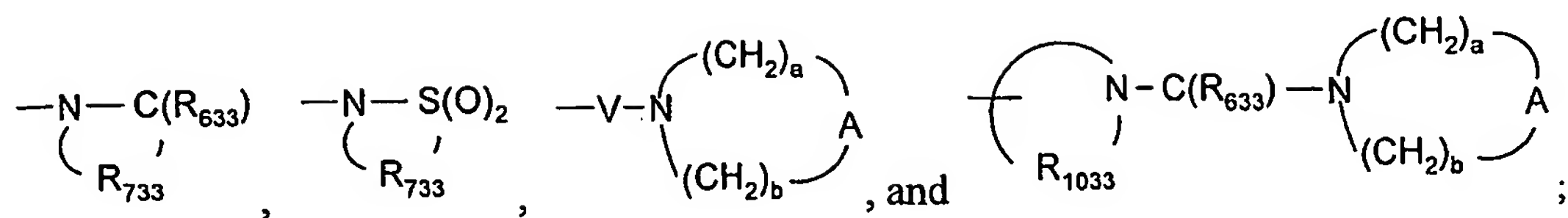
Y is selected from the group consisting of:

-S(O)<sub>0-2</sub>-,  
-S(O)<sub>2</sub>-N(R<sub>833</sub>)-,  
-C(R<sub>633</sub>)-,



each R<sub>433</sub> is independently selected from the group consisting of hydrogen, alkyl,  
 alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,  
 15 heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl  
 wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl,  
 heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and  
 heterocyclyl groups are unsubstituted or substituted by one or more substituents  
 independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl,  
 20 haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy,  
 arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino,  
 alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl,  
 alkynyl, and heterocyclyl, oxo;

R<sub>533</sub> is selected from the group consisting of:



each R<sub>633</sub> is independently selected from the group consisting of =O and =S;

each R<sub>733</sub> is independently C<sub>2-7</sub> alkylene;

each R<sub>833</sub> is independently selected from the group consisting of hydrogen, alkyl,

5 alkoxyalkylenyl, and arylalkylenyl;

each  $R_{933}$  is independently selected from the group consisting of hydrogen and

alkyl;

each R<sub>1033</sub> is independently C<sub>3-8</sub> alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -

10 N(R<sub>433</sub>)-;

each Q is independently selected from the group consisting of a bond,

-C(R<sub>633</sub>)-, -C(R<sub>633</sub>)-C(R<sub>633</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>633</sub>)-N(R<sub>833</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>833</sub>)-,

-C(R<sub>633</sub>)-O-, and -C(R<sub>633</sub>)-N(OR<sub>933</sub>)-;

V is selected from the group consisting of -C(R<sub>633</sub>)-, -O-C(R<sub>633</sub>)-,

15    -N(R<sub>833</sub>)-C(R<sub>633</sub>)-, and -S(O)<sub>2</sub>-; and

each W is independently selected from the group consisting of a bond, -C(O)-, and

$$-\text{S}(\text{O})_2^-;$$

with the proviso that when R<sub>A</sub> and R<sub>B</sub> form a fused heteroaryl or 5 to 7 membered saturated ring containing one heteroatom selected from the group consisting of N and S,

20 wherein the heteroaryl ring is unsubstituted or substituted by one or more R<sub>b</sub> groups, and

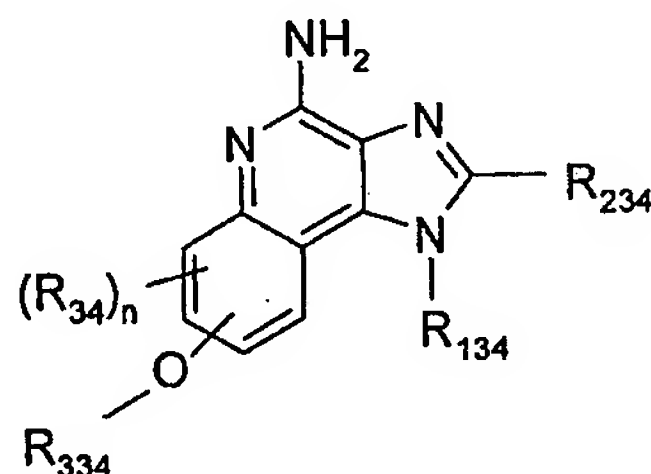
the 5 to 7 membered saturated ring is unsubstituted or substituted by one or more R<sub>c</sub>

groups, then  $R_{133}$  can also be

$$-X''-C(O)-N(R_{133}')(R_{133}'');$$

or a pharmaceutically acceptable salt thereof.

In another embodiment, the IRM compound can be chosen from aryloxy or arylalkyleneoxy substituted 1*H*-imidaz[4,5-*c*]quinoline-4-amines of the following Formula XXXIV:



XXXIV

wherein:

R<sub>334</sub> is selected from the group consisting of:

- Z-Ar,
- Z-Ar'-Y-R<sub>434</sub>,
- Z-Ar'-X-Y-R<sub>434</sub>,
- Z-Ar'-R<sub>534</sub>, and
- Z-Ar'-X-R<sub>534</sub>;

Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with -O-;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

$R_{34}$  is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

$n$  is 0 or 1;

$R_{134}$  is selected from the group consisting of:

- 5                     $-R_{434}$ ,  
                       $-X-R_{434}$ ,  
                       $-X-Y-R_{434}$ ,  
                       $-X-Y-X-Y-R_{434}$ , and  
                       $-X-R_{534}$ ;

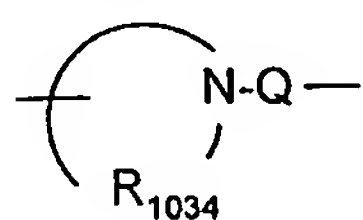
10                   $R_{234}$  is selected from the group consisting of:

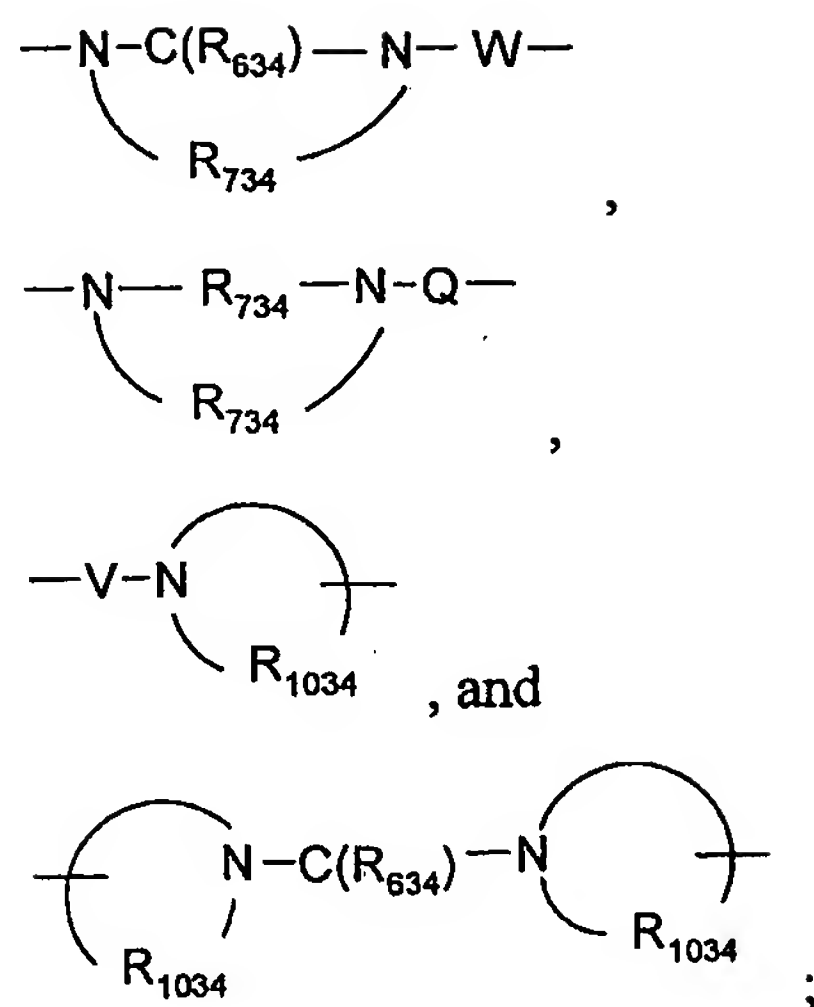
- $-R_{434}$ ,  
                       $-X-R_{434}$ ,  
                       $-X-Y-R_{434}$ , and  
                       $-X-R_{534}$ ;

15                  each  $X$  is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclylene or by one or more  $-O-$  groups;

                     each  $Y$  is independently selected from the group consisting of:

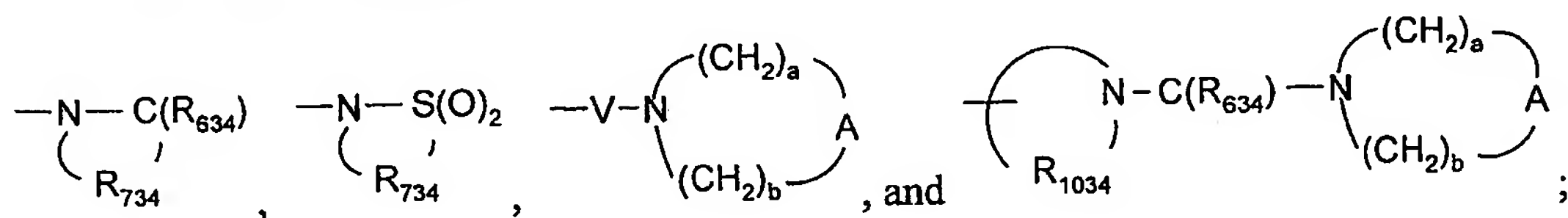
- 20                    $-S(O)_{0-2}-$ ,  
                       $-S(O)_2-N(R_{834})-$ ,  
                       $-C(R_{634})-$ ,  
                       $-C(R_{634})-O-$ ,  
                       $-O-C(R_{634})-$ ,  
 25                    $-O-C(O)-O-$ ,  
                       $-N(R_{834})-Q-$ ,  
                       $-C(R_{634})-N(R_{834})-$ ,  
                       $-O-C(R_{634})-N(R_{834})-$ ,  
                       $-C(R_{634})-N(OR_{934})-$ ,





- 5 each R<sub>434</sub> is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and
- 10 heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl,
- 15 alkynyl, and heterocyclyl, oxo;

each R<sub>534</sub> is independently selected from the group consisting of:



each R<sub>634</sub> is independently selected from the group consisting of =O and =S;

each R<sub>734</sub> is independently C<sub>2-7</sub> alkylene;

- 20 each R<sub>834</sub> is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each R<sub>934</sub> is independently selected from the group consisting of hydrogen and alkyl;

each R<sub>1034</sub> is independently C<sub>3-8</sub> alkylene;

each A is independently selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>434</sub>)-;

each Q is independently selected from the group consisting of a bond, -C(R<sub>634</sub>)-, -C(R<sub>634</sub>)-C(R<sub>634</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>634</sub>)-N(R<sub>834</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>834</sub>)-, -C(R<sub>634</sub>)-O-, and -C(R<sub>634</sub>)-N(OR<sub>934</sub>)-;

each V is independently selected from the group consisting of -C(R<sub>634</sub>)-, -O-C(R<sub>634</sub>)-, -N(R<sub>834</sub>)-C(R<sub>634</sub>)-, and -S(O)<sub>2</sub>-;

each W is independently selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

a and b are independently integers from 1 to 6 with the proviso that  $a + b \leq 7$ ; or a pharmaceutically acceptable salt thereof.

Herein, "non-interfering" means that the ability of the compound or salt to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substituent.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. Likewise, "alkylenyl", "alkenylenyl", and "alkynylenyl" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl,



trifluoromethyl, and the like. Similarly, the term "fluoroalkyl" is inclusive of groups that are substituted by one or more fluorine atoms, including perfluorinated groups (e.g., trifluoromethyl).

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems.

5 Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, 10 benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxaliny, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially 15 unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, homopiperazinyl, and the like.

20 The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

25 Unless otherwise specified, the aryl, heteroaryl, and heterocyclyl groups of Formulas IX - XXXIV can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, methylenedioxy, ethylenedioxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylthio, arylalkoxy, arylalkylthio, 30 heteroaryl, heteroaryloxy, heteroarylthio, heteroarylalkoxy, heteroarylalkylthio, amino, alkylamino, dialkylamino, heterocyclyl, heterocycloalkyl, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylcarbonyl,



heteroarylcarbonyl, heterocyclylcarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, aroyloxy, aroylthio, aroylamino, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl, alkylsulfonylamino, arylsulfonylamino, 5 arylalkylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino, heteroarylcarbonylamino, heteroarylalkylcarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl, 10 alkenylaminocarbonyl, heteroarylaminocarbonyl, heteroarylalkylaminocarbonyl, alkylaminocarbonylamino, alkenylaminocarbonylamino, arylaminocarbonylamino, arylalkylaminocarbonylamino, heteroarylaminocarbonylamino, heteroarylalkylaminocarbonylamino and, in the case of heterocyclyl, oxo. If any other groups are identified as being "substituted" or "optionally substituted", then those groups 15 can also be substituted by one or more of the above enumerated substituents.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula  $-N(R_{631})_2$  each  $R_{631}$  group is independently selected. In another example, when an  $R_{232}$  and an  $R_{332}$  group both contain 20 an  $R_{432}$  group, each  $R_{432}$  group is independently selected. In a further example, when more than one Y group is present (i.e.  $R_{232}$  and  $R_{332}$  both contain a Y group) and each Y group contains one or more  $R_{832}$  groups, then each Y group is independently selected, and each  $R_{832}$  group is independently selected.

In certain embodiments, the immune response modifier is selected from the group 25 consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolonaphthyridine amines, thiazolonaphthyridine amines, 30 pyrazolopyridine amines, pyrazoloquinoline amines, tetrahydropyrazoloquinoline amines, pyrazolonaphthyridine amines, tetrahydropyrazolonaphthyridine amines, 1*H*-imidazo

dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, and combinations thereof.

In certain embodiments, the immune response modifier is selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, and combinations thereof.

In certain embodiments, the immune response modifier is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, thioether substituted imidazopyridine amines, and combinations thereof.

In certain embodiments, the immune response modifier is selected from the group consisting of amide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, and combinations thereof.

### Cosolvents

Aqueous gel formulations of the invention include a water-miscible cosolvent. The water-miscible cosolvent assists in dissolving the immune response modifier in salt form. The cosolvent can be a single component or a combination. Examples of suitable

cosolvents include monopropylene glycol, dipropylene glycol, hexylene glycol, butylene glycol, glycerin, polyethylene glycol (of various molecular weights, e.g., 300 or 400), diethylene glycol monoethyl ether, and combinations thereof. Monopropylene glycol (i.e., propylene glycol) is particularly preferred as a cosolvent.

5           In certain embodiments, the cosolvent (or combination of cosolvents) is present in an amount of at least 10 wt-%, in other embodiments in an amount of greater than 25 wt-%, and in other embodiments at least 30 wt-%, based on the total weight of the aqueous gel. In certain embodiments, the cosolvent (or combination of cosolvents) is present in an amount of no greater than 90 wt-%, in other embodiments no greater than 80 wt-%, in  
10 other embodiments no greater than 70 wt-%, in other embodiments no greater than 60 wt-%, based on the total weight of the aqueous gel.

          In certain embodiments, water is present in an amount of at least 10 wt-%, in other embodiments at least 15 wt-%, in other embodiments at least 20 wt-%, and in other embodiments at least 25 wt-%, based on the total weight of the aqueous gel. In certain  
15 . embodiments, water is present in an amount of no greater than 95 wt-%, in other embodiments no greater than 90 wt-%, and in other embodiments no greater than 85 wt-%, based on the total weight of the aqueous gel.

### Thickeners

20           Aqueous gel formulations of the invention include a negatively charged thickener, preferably at least two negatively charged thickeners (typically of differing charge density). Preferably the thickeners are mucoadhesives. Examples of suitable negatively charged thickeners include: cellulose ethers such as carboxymethylcellulose sodium; polysaccharide gums such as xanthan gum; and acrylic acid polymers (i.e., homopolymers  
25 and copolymers) made from acrylic acid crosslinked with, for example, allyl sucrose or allyl pentaerythritol such as those polymers designated as carbomers in the United States Pharmacopoeia, and acrylic acid polymers made from acrylic acid crosslinked with divinyl glycol such as those polymers designated as polycarbophils in the United States Pharmacopoeia. Combinations of such thickeners can be used if desired.

30           In some embodiments of the invention, the negatively charged thickeners include carboxylic acid and/or carboxylate groups. Examples of such agents include carboxymethylcellulose sodium, xanthan gum, and the acrylic acid polymers. Preferably,

certain embodiments of the present invention include a combination of an acrylic acid polymer (i.e., polyacrylic acid polymer) and a polysaccharide gum (e.g., xanthan gum).

Carbomers are exemplary (and preferred) acrylic acid polymers. Suitable carbomers include, for example, those commercially available under the trade designation CARBOPOL (all available from Noveon, Inc., Cleveland, Ohio, USA). CARBOPOL polymers can provide a range of viscosities. For example, a 0.5 % solution of CARBOPOL 971P or CARBOPOL 941 has a viscosity of 4,000 – 11,000 cPs (pH 7.5, 25 °C, Brookfield viscometer at 20 rpm); a 0.5 % solution of CARBOPOL 934P or CARBOPOL 974P has a viscosity of 29,400 – 39,400 cPs (pH 7.5, 25 °C, Brookfield viscometer at 20 rpm); and a 0.5 % solution of CARBOPOL 940 or CARBOPOL 980 has a viscosity of 40,000 – 60,000 cPs (pH 7.5, 25 °C, Brookfield viscometer at 20 rpm). For certain embodiments, carbomers such as CARBOPOL 934P, CARBOPOL 974P, CARBOPOL 940, and CARBOPOL 980 are preferred. A particularly preferred carbomer is CARBOPOL 974P.

For certain embodiments, it is desirable to have a relatively highly crosslinked carbomer. Preferred relatively highly crosslinked carbomers include CARBOPOL 974P, CARBOPOL 940, and CARBOPOL 980. A particularly preferred relatively highly crosslinked carbomer is CARBOPOL 974P.

Suitable polycarbophils include, for example, those commercially available under the trade designation NOVEON polycarbophils (all available from Noveon, Inc., Cleveland, Ohio, USA). A preferred polycarbophil is NOVEON AA-1 USP Polycarbophil.

Various grades of carboxymethylcellulose sodium are commercially available that have differing aqueous viscosities. Aqueous 1% weight by volume (w/v) solutions with viscosities of 5-13,000 cps may be obtained. Examples include carboxymethylcellulose sodium, high viscosity, USP (CA194); carboxymethylcellulose sodium, medium viscosity, USP (CA192); and carboxymethylcellulose sodium, low viscosity, USP (CA193); all of which are available from Spectrum Chemicals and Laboratory Products, Inc., Gardena, CA, USA; and AKUCCELL AF 3085 (high viscosity), AKUCCELL AF 2785 (medium viscosity), and AKUCCELL AF 0305 (low viscosity), all of which are available from Akzo Nobel Functional Chemicals, Amersfoort, The Netherlands.

In certain embodiments, the thickener system includes a non-ionic thickener. Examples of suitable non-ionic thickeners include hydroxyethyl cellulose, hydroxymethyl cellulose, and hydroxypropyl cellulose. If included, the weight ratio of non-ionic thickener to negatively charged thickener (total weight of all negatively charged thickeners if more than one negatively charged thickener is included) is within the range of 1:4 to 1:10. In certain embodiments, the weight ratio is within the range of 1:4 to 1:7.

Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Examples include KLUCEL HF and KLUCEL MF, both of which are available from the Aqualon Division of Hercules Incorporated, Wilmington, Delaware, USA.

In certain embodiments, the thickener system includes a polysaccharide gum and an acrylic acid polymer. Preferably, the weight ratio of polysaccharide gum to acrylic acid polymer is within a range of 1:20 to 20:1. In certain embodiments, the weight ratio is within a range of 1:10 to 10:1, in other embodiments the weight ratio is within a range of 1:5 to 5:1, in other embodiments the weight ratio is within a range of 1:3 to 3:1, and in other embodiments the weight ratio is within a range of 1:2 to 2:1. A particularly preferred ratio is 1:2.

The thickener system is present in formulations of the invention in an amount sufficient to bring the viscosity to a level of at least than 1000 Centipoise (cps), preferably at least 5,000 cps, more preferably at least 8000 cps, and most preferably at least 10,000 cps. The viscosity is determined at  $20 \pm 0.5$  °C using a Haake RS series rheometer equipped with a 35 mm 2° cone using a controlled rate step test between 1 and  $80 \text{ s}^{-1}$  with an interpolation at  $16 \text{ s}^{-1}$  for viscosity versus shear rate.

In certain embodiments, the amount or concentration of the thickener system is at least 0.1 wt-%, in other embodiments at least 0.5 wt-%, in other embodiments at least 1.0 wt-%, and in other embodiments at least 1.5 wt-%, based on the total weight of the aqueous gel. In certain embodiments, the amount of the thickener system is no greater than 7 wt-%, in other embodiments no greater than 6 wt-%, in other embodiments no greater than 5 wt-%, and in other embodiments no greater than 4 wt-%, based on the total weight of the aqueous gel.

#### **pH Adjusting Agents and Buffers**



Aqueous gel formulations of the invention can additionally include a pharmaceutically acceptable pH adjusting agent to adjust the pH of the formulation to the desired range. Generally, the pH is at least 2, and preferably at least 3. Generally, the pH is no greater than 6, preferably no greater than 5, and more preferably no greater than 4.

5 The pH adjusting agent may be any pharmaceutically acceptable acid or base. Examples of suitable pH adjusting agents include hydrochloric acid, sodium hydroxide, tromethamine, and potassium hydroxide. Combinations of such agents can be used if desired.

Aqueous gel formulations of the invention can additionally include a

10 pharmaceutically acceptable buffer to maintain the pH of the formulations in the desired range (preferably, 2 to 6, and more preferably, 3 to 4). The buffer may be any pharmaceutically acceptable buffer that provides one or more of the desired pH ranges. Examples of suitable buffers include buffers containing lactic acid, tartaric acid, citric acid, and succinic acid. Combinations of buffers can be used if desired. The buffers can

15 also function as tonicity adjusting agents.

### Preservatives

Aqueous gel formulations of the invention can additionally include a preservative. The preservative includes one or more compounds that inhibit microbial growth (e.g.,

20 fungal and bacterial growth) within the composition. Suitable preservatives are water soluble and include quaternary ammonium compounds (e.g., benzalkonium chloride), benzethonium chloride, parabens (e.g., methylparaben, propylparaben), boric acid, isothiazolinone, organic acids (e.g., sorbic acid), alcohols (e.g., phenyl ethyl alcohol, cresol, chlorobutanol, benzyl alcohol), carbamates, chlorhexidine, and combinations

25 thereof. Preferably, the preservative is methylparaben, propylparaben, or combinations thereof. Certain water-miscible cosolvents, such as glycerin or propylene glycol, also have antimicrobial properties.

In certain embodiments, the preservative (or combination of preservatives) is present in an amount of at least 0.005 wt-%, in other embodiments at least 0.01 wt-%, in

30 other embodiments at least 0.015 wt-%, and in other embodiments at least 0.02 wt-%, based on the total weight of the aqueous gel. In certain embodiments, the preservative (or combination of preservatives) is present in an amount of no greater than 1.0 wt-%, in other

embodiments at most 0.75 wt-%, in other embodiments at most 0.5 wt-%, and in other embodiments no greater than 0.4 wt-%, based on the total weight of the aqueous gel.

### Chelating agents

5       Aqueous gel formulations of the invention can additionally include a chelating agent. Chelating agents are compounds that complex metal ions. Examples of suitable chelating agents include ethylenediaminetetracetic acid (EDTA) and derivatives thereof such as the disodium salt, ethylenediaminetetracetic acid disodium salt dehydrate, and combinations thereof. Preferably, the chelating agent is ethylenediaminetetracetic acid  
10       disodium salt dihydrate (edetate disodium).

      In certain embodiments, the chelating agent (or combination of chelating agents) is present in an amount of at least 0.001 wt-%, in other embodiments at least 0.01 wt-%, and in other embodiments at least 0.02 wt-%, based on the total weight of the aqueous gel. In certain embodiments, the chelating agent (or combination of chelating agents) is present in  
15       an amount of no greater than 2.0 wt-%, in other embodiments no greater than 1.5 wt-%, and in other embodiments no greater than 1.0 wt-%, based on the total weight of the aqueous gel.

### Applications

20       Aqueous gel formulations of the present invention can be used to treat or prevent conditions associated with mucosal tissue. In some embodiments, the invention provides methods that are particularly advantageous for the topical application to the cervix for treatment of cervical conditions such as cervical dysplasias including dysplasia associated with human papillomavirus (HPV), low-grade squamous intraepithelial lesions, high-grade  
25       squamous intraepithelial lesions, atypical squamous cells of undetermined significance (typically, with the presence of high-risk HPV), and cervical intraepithelial neoplasia (CIN).

      The present invention also provides methods of treating a mucosal associated condition. Alternatively stated, the present invention provides methods of treating a  
30       condition associated with mucosal tissue.

In the methods of the present invention, the aqueous gels of the present invention may be applied once a week or several times a week. For example, the aqueous gel may be applied twice a week, three times a week, five times a week, or even daily.

In the methods of the present invention, the applications of the aqueous gels of the present invention may extend for a total time period of at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, or more, depending on the desired treatment regimen.

The actual dosing (treatment) regimen used for a given condition or subject may depend at least in part on many factors known in the art, including, but not limited to, the physical and chemical nature of the IRM compound, the nature of the delivery material, the amount of the IRM compound being administered, the state of the subject's immune system (e.g., suppressed, compromised, stimulated), the method of administering the IRM compound, and the species to which the IRM compound is being administered.

The methods of the present invention may be applicable for any suitable subject. Suitable subjects include, but are not limited to, animals such as, but not limited to, humans, non-human primates, rodents, dogs, cats, horses, pigs, sheep, goats, cows, or birds.

The methods of the present invention are suitable for a variety of medical objectives, including therapeutic, prophylactic (e.g., as a vaccine adjuvant), or diagnostic. As used herein, "treating" a condition or a subject includes therapeutic, prophylactic, and diagnostic treatments.

The term "an effective amount" (e.g., therapeutically or prophylactically) means an amount of the compound sufficient to induce a desired (e.g., therapeutic or prophylactic) effect, such as cytokine induction, inhibition of TH2 immune response, antiviral or antitumor activity, reduction or elimination of neoplastic cells. The amount of the IRM compound that will be therapeutically effective in a specific situation will depend on such things as the activity of the particular compound, the dosing regimen, the application site, the particular formulation and the condition being treated. As such, it is generally not practical to identify specific administration amounts herein; however, those skilled in the art will be able to determine appropriate therapeutically effective amounts based on the guidance provided herein and information available in the art pertaining to these compounds.



The aqueous gels of the present invention may be used for the application of an IRM compound to the affected area of a subject for treating a dermal and/or mucosal condition. Examples of such conditions include herpes, keloids, warts, molluscum, or combinations thereof. It will be understood by one of skill in the art that such conditions  
5 (e.g., warts) can be on both mucosal and dermal tissue.

The aqueous gels of the present invention may be used for the application of an IRM compound to mucosal tissue for the treatment of a mucosal associated condition.

As used herein, a "mucosal associated condition" means an inflammatory, infectious, neoplastic, or other condition that involves mucosal tissue or that is in  
10 sufficient proximity to a mucosal tissue to be affected by a therapeutic agent topically applied to the mucosal tissue. Examples of such conditions include a papilloma virus infection of the cervix, cervical dysplasias including dysplasia associated with human papillomavirus (HPV), low-grade squamous intraepithelial lesions, high-grade squamous  
intraepithelial lesions, atypical squamous cells of undetermined significance (typically,  
15 with the presence of high risk HPV), and cervical intraepithelial neoplasia, an atopic allergic response, allergic rhinitis, a neoplastic lesion, and a premalignant lesion.

As used herein, "mucosal tissue" includes mucosal membranes such as buccal, gingival, nasal, ocular, tracheal, bronchial, gastrointestinal, rectal, urethral, ureteral, vaginal, cervical, and uterine mucosal membranes. For example, one could treat oral  
20 lesions, vaginal lesions, or anal lesions by the methods described. One could also use the methods in combination with mucosal application of vaccines.

In one embodiment, the IRM compound can be applied to vaginal or supravaginal mucosal tissue for the treatment of a cervical dysplasia. In other embodiments, an IRM can be applied to the mucosal tissue of the rectum for the treatment of, e.g., anal canal  
25 condyloma.

Cervical dysplasias to be treated by the methods of the present invention preferably include dysplastic conditions such as low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, atypical squamous cells of undetermined  
significance (typically, with the presence of high-risk HPV), and cervical intraepithelial  
30 neoplasia (CIN).

Approximately 16,000 new cases of invasive cancer of the cervix are diagnosed each year in the U.S. despite extensive screening of women to detect predictive cellular

changes. There are also about 3,000 deaths due to cervical cancer in the U.S. alone and this is usually secondary to not detecting the primary cancerous lesion in a timely manner.

The Papanicolaou Test (Pap smear) is the screening test that has been accepted since the 1950s as the method to detect abnormal cells of the cervix, including  
5 inflammation and dysplasia, which includes cervical cancer. This screening test has been widely adopted in industrialized countries and has had a profound impact on mortality associated with cervical cancers. An abnormal Pap smear prompts close observation for disease progression with the potential for the therapeutic interventions of destruction or excision of cancerous or pre-cancerous tissues. These excisional treatments are expensive,  
10 uncomfortable and associated with failure rates that range from 2% to 23% and with higher failure rates reported for the more advanced lesions. Failure rates have recently been documented to approximate 10% following laser treatment.

The etiologic agent for cervical cancer was originally thought to be the herpes virus. However, there was a gradual shift from this focus on herpes virus to the human  
15 papillomavirus (HPV). Improved experimental methods over the recent past have allowed the characterization of a full spectrum of HPV subtypes, which has resulted in the conclusion that the high risk HPV types (e.g., HPV 16, 18, and less frequently 31, 33, 35, 45) are very likely the exclusive initiating factor (i.e., oncogenic agent) for cervical dysplasia and subsequent cancers. The mechanism of HPV transformation of the normal  
20 cell to a dysplastic cell is associated with the HPV encoded oncoproteins (E6 and E7) from the high risk genotypes binding the cell's tumor suppressor gene products p53 and Rb resulting in disruption of the cell cycle control mechanism in which p53 and Rb play an important role. In addition, the application of these molecular methods has resulted in the epidemiologic observation that HPV is isolated from approximately 93% of cervical  
25 tumors, which has further strengthened the generally accepted conclusion that HPV infection is the most important initiating agent for cervical cancer.

Exposure to HPV is common in sexually active women, but it does not invariably lead to dysplasia or cancer in most of the exposed women. Infected women who harbor persistent viral DNA have about five times the chance of persistent dysplasia compared to  
30 women who are able to eradicate the virus. The importance of cell-mediated immune response to HPV infection is illustrated by the observation that the antibody mediated immune response is not effective in eliminating established infections as is demonstrated

by the fact that patients with invasive cervical cancer often exhibit high antibody levels against the viral E6 and E7 proteins. This particular antibody response probably reflects extensive antigen exposure in the face of increasing tumor burden. In contrast to the apparently inconsequential effect of the humoral immune response; the cell-mediated  
5 immune response (Th-1-Type Response) appears to be effective in controlling tumor progression. Regression of intraepithelial lesions is accompanied by a cellular infiltrate consisting of CD4<sup>+</sup> T-cells, CD8<sup>+</sup> T-cells, natural killer cells (NK) and macrophages. This inflammatory infiltrate was usually associated with tumor regression that is in contrast to women who lack the ability to mount this inflammatory response and who experience  
10 disease progression. In addition, patients with a defect in cell-mediated immunity have increased cervical cancer rates, whereas those with defects in the production of antibody do not exhibit the same susceptibility.

Aqueous gels of the present invention may be applied to mucosal tissue with the use of a delivery device. Suitable devices include barrel type applicators, cervical caps,  
15 diaphragms, and solid matrices such as tampons, cotton sponges, cotton swabs, foam sponges, and suppositories. The IRM can be removed by withdrawing the device from contact with the mucosal tissue, if desired.

In some embodiments the device can be used in combination with the aqueous gel formulation. In one embodiment, a gel containing an IRM compound can be placed into  
20 the concave region of a cervical cap, which is then place directly over the cervix. In another embodiment, a cotton or foam sponge can be used in combination with an aqueous gel of the present invention.

In some embodiments, an applicator may be used to place the device and/or gel in the proper location on the mucosal tissue. Examples of such applicators include, for  
25 example, paperboard or plastic tube applicators commonly used for inserting tampons or suppositories. A preferred applicator is a barrel type applicator, which may be prefilled or supplied in a kit together with a container of gel and filled by the patient.

## EXAMPLES

30 The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as

well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

The IRMs used to prepare the gels in the following examples are shown in Table 1.

Table 1		
IRM	Chemical Name	Reference
IRM1	4-(4-amino-2-propyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl)- <i>N</i> -propylbutyramide	International Publication No. WO2005/094531 Example 2
IRM2	<i>N</i> -[2-(4-amino-7-benzyloxy-2-ethoxymethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl)-1,1-dimethylethyl]acetamide	International Publication No. WO2005/020999 Example 142
IRM3	3-(4-amino-2-propyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl)propionamide hydrochloride	International Publication No. WO2005/094531 Example 18
IRM4	<i>N</i> -[2-(4-amino-2-ethoxymethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl)ethyl]- <i>N'</i> -isopropylurea	U.S. Patent No. 6,541,485 <sup>#</sup>
IRM5	<i>N</i> -[4-(4-amino-2-butyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl)butyl]methanesulfonamide	U.S. Patent No. 6,331,539 Example 6
IRM6	<i>N</i> -{4-[4-amino-2-(2-methoxyethyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl]butyl}methanesulfonamide	U.S. Patent No. 6,331,539 Example 111
IRM7	1-(2-methylpropyl)-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-4-amine (imiquimod)	U.S. Patent No. 4,689,338 Example 99
IRM8	2-propylthiazolo[4,5- <i>c</i> ]quinolin-4-amine hydrochloride	U.S. Patent No. 6,110,929 Example 14

5 <sup>#</sup>IRM4 is not specifically exemplified but can be readily prepared using the synthetic methods disclosed in the cited reference.

## TEST METHOD

10 In the examples below the serum and intravaginal cytokine data were obtained using the following general test method.

Rats were acclimated to collars (Lomir Biomedical, Malone, NY) around the neck on two consecutive days prior to actual dosing. Rats were collared to prevent ingestion of the drug. Animals were then dosed intravaginally with 50  $\mu$ L of gel. Single dosed rats received one intravaginal dose with samples collected at various times following dosing.

15 Multiple dosed rats were dosed as described in the examples below with samples collected

at various times following the final dose. Blood was collected by cardiac puncture. Blood was allowed to clot briefly at room temperature and serum was separated from the clot via centrifugation. The serum was stored at  $-20^{\circ}\text{C}$  until it was analyzed for cytokine concentrations.

5        Following blood collection, the rats were euthanized and their vaginal tract, including the cervix, was then removed and the tissue was weighed, placed in a sealed 1.8 mL cryovial and flash frozen in liquid nitrogen. The frozen vaginal tissue sample was then suspended in 1.0 mL of RPMI medium (Celox, St. Paul, MN) containing 10% fetal bovine serum (Atlas, Fort Collins, CO), 2 mM L-glutamine, penicillin/streptomycin and 2-  
10       mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, CA). The tissue was homogenized using a Tissue Tearor (Biospec Products, Bartlesville, OK) for approximately one minute. The tissue suspension was then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet the debris, and the supernatant collected and stored at  $-20^{\circ}\text{C}$  until analyzed for cytokine  
15       concentrations.

ELISA kits for rat tumor necrosis factor-alpha (TNF) were purchased from BD PharMingen (San Diego, CA) and the rat monocyte chemoattractant protein-1 (MCP-1) ELISA kits were purchased from BioSource Intl. (Camarillo, CA). Both kits were performed according to manufacturer's specifications. Results for both TNF and MCP-1  
20       are expressed in pg/mL and are normalized per 200 mg of tissue. The sensitivity of the TNF ELISA, based on the lowest value used to form the standard curve, is 32 pg/mL and for the MCP-1 ELISA it is 12 pg/mL.

#### Examples 1 and 2

25        The gels shown in Table 2 below were prepared using the following method.

Step 1: The parabens were dissolved in the propylene glycol.

Step 2: The IRM was combined with the aqueous ethanesulfonic acid and a portion of the water.

Step 3: The solution from step 1 was combined with the mixture from step 2.

30        Step 4: Edetate disodium was dissolved in water. The carbomer was added to the solution and stirred until well hydrated.

Step 5: The dispersion from step 4 was combined with the mixture from step 3.



Step 6: 20% tromethamine was added to adjust the pH.

Step 7: Sufficient water was added to adjust the final weight and the gel was mixed well.

Table 2		
Ingredient	Gels (% w/w)	
	Ex 1 IRM1	Ex 2 IRM2
IRM	0.1	0.1
0.25 N ethanesulfonic acid	0.594	0.452
Carbomer 974P	2.1	2.1
Propylene glycol	15	15
Methylparaben	0.15	0.15
Propylparaben	0.03	0.03
Edetate disodium	0.05	0.05
20% Tromethamine solution	1.5	1.5
Purified water	80.48	80.62
pH	3.95	4.07

### Example 3

The gel shown in Table 3 below was prepared using the following method.

Step 1: The parabens were dissolved in the propylene glycol.

Step 2: IRM3 was combined with a portion of the water.

Step 3: The solution from step 1 was combined with the mixture from step 2 and heated to

55°C and ultrasonicated.

Step 4: Edetate disodium was dissolved in water. The carbomer was added to the solution and stirred until well hydrated.

Step 5: The dispersion from step 4 was combined with the mixture from step 3.

Step 6: 20% tromethamine was added to adjust the pH.

Step 7: Sufficient water was added to adjust the final weight and the gel was mixed well.

Table 3	
Ingredient	(% w/w)
IRM 3	0.1
Carbomer 974P	2.1
Propylene glycol	15
Methylparaben	0.15
Propylparaben	0.03
Edetate disodium	0.05
20% Tromethamine solution	1.5
Purified water	80.65
pH	3.99

The ability of the gels of Examples 1 - 3 to induce cytokines was determined using the test method described above. The animals received an intravaginal dose once a day on day 0 and on day 3 for a total of 2 doses. The results are shown in Table 4 below where  
5 each value is the mean of 3 animals  $\pm$  SEM (standard error of the mean).

Table 4					
Time (hours) Post Dose	Gel	Cytokine Concentrations			
		TNF (pg/mL)		MCP-1 (pg/mL)	
		Serum	Tissue	Serum	Tissue
2	Example 1	36 $\pm$ 18	356 $\pm$ 14	136 $\pm$ 23	226 $\pm$ 35
2	Example 2	84 $\pm$ 16	1736 $\pm$ 794	147 $\pm$ 33	588 $\pm$ 221
2	Example 3	97 $\pm$ 6	568 $\pm$ 458	114 $\pm$ 33	282 $\pm$ 192
4	Example 1	53 $\pm$ 10	273 $\pm$ 172	77 $\pm$ 28	501 $\pm$ 291
4	Example 2	79 $\pm$ 6	1064 $\pm$ 290	15 $\pm$ 15	1839 $\pm$ 113
4	Example 3	49 $\pm$ 9	188 $\pm$ 48	161 $\pm$ 13	637 $\pm$ 252
6	Example 1	44 $\pm$ 3	210 $\pm$ 19	161 $\pm$ 38	756 $\pm$ 205
6	Example 2	73 $\pm$ 10	743 $\pm$ 211	260 $\pm$ 14	1857 $\pm$ 276
6	Example 3	56 $\pm$ 13	105 $\pm$ 37	218 $\pm$ 63	444 $\pm$ 298
4	<sup>1</sup> Vehicle	101 $\pm$ 32	94 $\pm$ 10	173 $\pm$ 20	176 $\pm$ 59

<sup>1</sup>Vehicle (2.1 % carbomer 974, 15 % propylene glycol, 0.15 % methylparaben, 0.03 % propylparaben, 0.05 % edetate sodium, 1.35% 20% tromethamine solution, and 81.32 % water)

10

#### Examples 4 – 6

The gels in Table 5 below were prepared using the following general method.

Step 1: The parabens were dissolved in the propylene glycol.

Step 2: IRM4 was dissolved in the aqueous ethanesulfonic acid.

15 Step 3: The solution from step 1 was combined with the solution from step 2.

Step 4: Edetate disodium was dissolved in water. The carbomer and xanthan gum, if used, were added to the solution and stirred until well hydrated.

Step 5: The dispersion from step 4 was combined with the solution from step 3.

Step 6: 20% tromethamine was added to adjust the pH.

5 Step 7: Sufficient water was added to adjust the final weight and the gel was mixed well.

Table 5			
Ingredient	Gels (% w/w)		
	Ex 4	Ex 5	Ex 6
IRM4	0.01	0.1	1
0.5 N ethanesulfonic acid	0.054	0.54	5.4
Carbomer 974P	1.7	1.7	2
Xanthan gum	0.0	0.0	0.56
Propylene glycol	15	15	30
Methylparaben	0.15	0.15	0.15
Propylparaben	0.03	0.03	0.03
Edetate disodium	0.05	0.05	0.05
20% Tromethamine solution	0.7	0.5	1.9
Purified water	82.31	81.93	58.91
pH	3.9	3.9	4.3

The ability of the gels of Examples 4 - 6 to induce cytokines following a single dose was determined using the test method described above. The results are shown in

10 Table 6 below where each value is the mean of 5 animals  $\pm$  SEM.



Table 6					
Time (hours) Post Dose	Gel	Cytokine Concentrations			
		TNF (pg/mL)		MCP-1 (pg/mL)	
		Serum	Tissue	Serum	Tissue
2	Example 4	16±2	331±24	96±4	134±57
2	Example 5	19±6	433±64	91±11	298±104
2	Example 6	45±21	853±150	90±6	501±111
4	Example 4	11±6	257±9	115±10	112±41
4	Example 5	30±6	397±32	123±13	462±159
4	Example 6	70±32	700±86	103±9	866±150
8	Example 4	13±5	297±11	142±13	283±84
8	Example 5	21±5	275±21	146±16	337±96
8	Example 6	14±2	557±232	171±23	641±144
4	<sup>1</sup> Vehicle	37±14	255±15	108±16	9±3

<sup>1</sup>Vehicle (2 % carbomer 974, 30 % propylene glycol, 0.15 % methylparaben, 0.03 % propylparaben, 0.05 % edetate sodium, 0.3% of 20% tromethamine solution, and 67.47 % water)

5

#### Examples 7 and 8

The gels shown in Table 7 were prepared using the following general method.

Step 1: IRM2 was combined with the aqueous ethanesulfonic acid and a portion of the water. The combination was mixed until the IRM was dissolved.

Step 2: The parabens were dissolved in the propylene glycol.

10 Step 3: Edetate sodium was dissolved in water. The carbomer was added and the mixture was stirred until the carbomer was hydrated.

Step 4: The solution from step 2 was added to the solution from step 1 and the combination was mixed until uniform.

15 Step 5: The dispersion from step 3 was added to the solution from step 4 and the combination was mixed until a uniform, smooth gel was obtained.

Step 6: Sufficient 20% tromethamine was added to adjust the pH to about 4.

Step 7: Sufficient water was added to adjust the final weight and the gel was mixed well until uniform.

Table 7		
Ingredient	Gels (% w/w)	
	Ex 7	Ex 8
IRM2	0.01	0.1
Ethanesulfonic acid (0.5M + 5% extra)	0.0455	0.455
Carbomer 974P	2.1	2.1
Propylene glycol	15	15
Methylparaben	0.15	0.15
Propylparaben	0.03	0.03
Edetate disodium	0.05	0.05
20% Tromethamine solution	qs pH 4	qs pH 4
Purified water	qs 100	qs 100
pH	4.1	4.2

### Example 9

The gel shown in Table 8 was prepared using the following general method.

- Step 1: IRM2 was combined with the aqueous ethanesulfonic acid and a portion of the  
5 water. The combination was mixed until the IRM was dissolved.
- Step 2: The parabens were dissolved in the propylene glycol.
- Step 3: Edetate sodium was dissolved in water. The carbomer was added and the mixture was stirred until the carbomer was hydrated.
- Step 4: The solution from step 2 was added to the solution from step 1 and the  
10 combination was mixed until uniform.
- Step 5: The dispersion from step 3 was added to the solution from step 4. The combination was mixed well resulting in a milky, fluid dispersion.
- Step 6: Sufficient 20% tromethamine was added to adjust the pH to about 4 and the dispersion thickened and foamed.
- 15 Step 7: Xanthan gum was mixed with water and then added to the dispersion from step 6. The mixture was heated at 50 °C with stirring for 4 hours. The gel was allowed to cool to ambient temperature overnight with stirring.

Table 8	
Ingredient	(% w/w)
IRM4	1
Ethanesulfonic acid (0.5M + 5% extra)	4.565
Carbomer 974P	2.1
Xanthan gum	0.2
Propylene glycol	15
Methylparaben	0.15
Propylparaben	0.03
Edetate disodium	0.05
20% Tromethamine solution	qs pH 4
Purified water	qs 100
pH	4.0

The ability of the gels of Examples 7 - 9 to induce cytokines following a single dose was determined using the test method described above. The gel of Example 9 was stirred prior to dosing to minimize air bubbles. The results are shown in Table 9 below where each value is the mean of 6 animals  $\pm$  SEM.

Table 9					
Time (hours) Post Dose	Gel	Cytokine Concentrations			
		TNF (pg/mL)		MCP-1 (pg/mL)	
		Serum	Tissue	Serum	Tissue
0.5	Example 7	159 $\pm$ 49	315 $\pm$ 63	212 $\pm$ 66	34 $\pm$ 1
0.5	Example 8	716 $\pm$ 341	288 $\pm$ 22	239 $\pm$ 57	59 $\pm$ 21
0.5	Example 9	359 $\pm$ 220	375 $\pm$ 85	130 $\pm$ 33	39 $\pm$ 2
1	Example 7	199 $\pm$ 76	343 $\pm$ 79	110 $\pm$ 39	41 $\pm$ 7
1	Example 8	237 $\pm$ 123	340 $\pm$ 93	156 $\pm$ 65	34 $\pm$ 2
1	Example 9	306 $\pm$ 160	681 $\pm$ 222	119 $\pm$ 40	74 $\pm$ 30
4	Example 7	165 $\pm$ 50	915 $\pm$ 175	261 $\pm$ 64	476 $\pm$ 127
4	Example 8	105 $\pm$ 10	1165 $\pm$ 250	247 $\pm$ 32	1098 $\pm$ 307
4	Example 9	233 $\pm$ 144	1628 $\pm$ 202	254 $\pm$ 38	1217 $\pm$ 271
8	Example 7	133 $\pm$ 18	1190 $\pm$ 368	279 $\pm$ 27	583 $\pm$ 67
8	Example 8	166 $\pm$ 51	1029 $\pm$ 268	259 $\pm$ 36	923 $\pm$ 131
8	Example 9	159 $\pm$ 44	1336 $\pm$ 149	325 $\pm$ 44	1895 $\pm$ 254
4	<sup>1</sup> Vehicle	125 $\pm$ 0	642 $\pm$ 101	191 $\pm$ 39	88 $\pm$ 41

<sup>1</sup>Vehicle (2.1 % carbomer 974, 0.4 % xanthan gum, 15 % propylene glycol, 0.15 % methylparaben, 0.03 % propylparaben, 0.05 % edetate sodium, 20% tromethamine solution qs to pH 4.0, and water qs to 100%)

10

## Examples 10 and 11

The gels shown in Table 10 were prepared using the following general method.

Step 1: The IRM was combined with the aqueous ethanesulfonic acid and the combination was mixed until the IRM was dissolved.

Step 2: The parabens were dissolved in the propylene glycol.

Step 3: Edetate sodium was dissolved in the bulk of the water. The carbomer was added  
5 and the mixture was stirred until the carbomer was hydrated.

Step 4: The solution from step 2 was added to the solution from step 1 and the combination was mixed until uniform.

Step 5: The dispersion from step 3 was added in portions to the solution from step 4 and the combination was mixed well.

10 Step 6: 20% tromethamine was added to adjust the pH to about 4.

Step 7: Sufficient water was added to adjust the final weight and the gel was mixed well until uniform.

Table 10		
Ingredient	Gels (% w/w)	
	Ex 10	Ex 11
IRM	0.05 IRM5	0.5 IRM6
Ethanesulfonic acid (0.05 N)	2.76	0
Ethanesulfonic acid (0.02 N)	0	6.8
Carbomer 974P	3.3	3.5
Propylene glycol	15	15
Methylparaben	0.15	0.15
Propylparaben	0.03	0.03
Edetate disodium	0.05	0.05
20% Tromethamine solution	3.2	4.5
Purified water	qs 100	qs 100
pH	*	4.4

\*Not measured

The ability of the gels of Examples 10 and 11 to induce cytokines following a  
15 single dose was determined using the test method described above except that the dose was 100  $\mu$ L instead of 50 $\mu$ L. The results are shown in Table 11 below where each value is the mean of 3 animals  $\pm$  SEM (standard error of the mean).

Table 11					
Time (hours) Post Dose	Gel	Cytokine Concentrations			
		TNF (pg/mL)		MCP-1 (pg/mL)	
		Serum	Tissue	Serum	Tissue
2	Example 10	0 ± 0	230 ± 23	83 ± 7	276 ± 27
2	Example 11	33 ± 33	101 ± 28	96 ± 7	31 ± 4
4	Example 10	0 ± 0	169 ± 52	123 ± 36	411 ± 241
4	Example 11	0 ± 0	214 ± 19	87 ± 6	197 ± 72
2	Untreated	0 ± 0	90 ± 17	77 ± 7	26 ± 2

### Example 12

The gel shown in Table 12 was prepared using the following general method.

- Step 1: IRM7 was combined with the aqueous methanesulfonic acid and mixed. Water  
5 was added in portions until the IRM was completely dissolved.
- Step 2: The edetate sodium was dissolved in the bulk of the water.
- Step 3: The hydroxypropyl cellulose was combined with propylene glycol (about two thirds of the amount used to achieve the final weight percent) and the combination was mixed to form a slurry.
- 10 Step 4: The carbomer was slowly added to the solution from step 2. The mixture was stirred until the carbomer was fully hydrated.
- Step 5: The slurry from step 3 was added to the mixture from step 4 and mixed thoroughly.
- Step 6: The parabens were dissolved in propylene glycol (about one third of the amount  
15 used to achieve the final weight percent).
- Step 7: The solution from step 6 was added to the solution from step 1 and thoroughly mixed.
- Step 8: The solution from step 7 was slowly added to the mixture from step 5 with mixing.
- 20 Step 9: 20% tromethamine was added to adjust the pH to 4.

Table 12	
Ingredient	(% w/w)
IRM7	0.05
Methanesulfonic acid (0.15 M)	14.6
Carbomer 974P	3.5
<sup>1</sup> Hydroxypropyl cellulose	0.50
Propylene glycol	15
Methylparaben	0.15
Propylparaben	0.03
Edetate disodium	0.05
20% Tromethamine solution	qs pH 4
Purified water	qs 100
pH	4.0

<sup>1</sup>KLUCEL HF

## Examples 13 – 15

The gels in Table 13 below were prepared using the following general method.

- 5 Step 1: The parabens were dissolved in propylene glycol (about one third of the amount used to achieve the final weight percent).
- Step 2: IRM8 and a small portion of the water were added to the solution from step 1. The mixture was stirred until the IRM was completely dissolved.
- Step 3: The edetate sodium was dissolved in the bulk of the water.
- 10 Step 4: The hydroxypropyl cellulose was slowly added with stirring to propylene glycol (about two thirds of the amount used to achieve the final weight percent).
- Step 5: The mixture from step 4 was added to the solution from step 3.
- Step 6: The carbomer was slowly added with stirring to the mixture from step 5. Stirring was continued until the carbomer was fully hydrated.
- 15 Step 7: About half of the 20 % tromethamine solution was slowly added with stirring to the mixture from step 6.
- Step 8: The solution from step 2 was slowly added with stirring to the mixture from step 7.
- Step 9: The remainder of the 20 % tromethamine solution was slowly added with stirring
- 20 to the mixture from step 8. Stirring was continued until a uniform gel was obtained.

Table 13			
Ingredient	Gels (% w/w)		
	Ex 13	Ex 14	Ex 15
IRM8	0.0574	0.574	1.148
Carbomer 974P	2.00	3.50	3.50
Hydroxypropyl cellulose (HF grade)	0.50	0.50	0.50
Propylene glycol	15.0	15.0	15.0
Methylparaben	0.15	0.15	0.15
Propylparaben	0.03	0.03	0.03
Edetate disodium	0.05	0.05	0.05
20% Tromethamine solution	0.94	3.47	5.00
Purified water	qs 100	qs 100	qs 100

### Example 16

The gel shown in Table 14 below was prepared using the following general method of Examples 13 – 15 except that all of the 20% tromethamine solution was added in step 7.

Table 14	
Ingredient	(% w/w)
IRM8	0.00574
Carbomer 974P	2.0
Hydroxypropyl cellulose (HF grade)	0.5
Propylene glycol	15.0
Methylparaben	0.15
Propylparaben	0.03
Edetate disodium	0.05
20% Tromethamine solution	0.94
Purified water	qs 100
pH	4.0

5

The ability of the gels of Examples 13 - 16 to induce cytokines following a single dose was determined using the test method described above except that the dose was 100  $\mu$ L instead of 50 $\mu$ L. The results are shown in Table 15 below where each value is the mean of 6 animals  $\pm$  SEM (standard error of the mean).



Table 15					
Time (hours) Post Dose	Gel	Cytokine Concentrations			
		TNF (pg/mL)		MCP-1 (pg/mL)	
		Serum	Tissue	Serum	Tissue
2	Example 16	2 ± 1	214 ± 29	83 ± 12	315 ± 122
2	Example 13	0 ± 0	285 ± 52	115 ± 25	609 ± 111
2	Example 14	2 ± 1	328 ± 18	98 ± 13	895 ± 132
2	Example 15	3 ± 1	428 ± 27	95 ± 21	1202 ± 72
2	<sup>1</sup> Vehicle	7 ± 5	159 ± 18	94 ± 16	47 ± 7
4	Example 16	0 ± 0	234 ± 34	118 ± 21	727 ± 172
4	Example 13	5 ± 3	196 ± 26	121 ± 9	1027 ± 81
4	Example 14	2 ± 1	246 ± 32	166 ± 33	1422 ± 120
4	Example 15	0 ± 0	246 ± 25	175 ± 40	1257 ± 224
4	<sup>1</sup> Vehicle	0 ± 0	155 ± 25	117 ± 15	30 ± 3
6	Example 16	0 ± 0	110 ± 10	160 ± 16	457 ± 88
6	Example 13	2 ± 2	151 ± 19	137 ± 34	574 ± 71
6	Example 14	1 ± 0	191 ± 37	188 ± 43	1121 ± 213
6	Example 15	3 ± 3	177 ± 24	221 ± 27	1183 ± 139
6	<sup>1</sup> Vehicle	8 ± 5	117 ± 26	148 ± 16	28 ± 4

<sup>1</sup>Vehicle (2.00 % carbomer 974, 0.50 % hydroxypropyl cellulose, 15.0 % propylene glycol, 0.15 % methylparaben, 0.03 % propylparaben, 0.05 % edetate sodium, 0.94 % 20% tromethamine solution, and water qs to 100%)

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The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

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## WHAT IS CLAIMED IS:

1. An aqueous gel comprising:  
water;  
an immune response modifier (IRM) other than 1-(2-methylpropyl)-1*H*-  
5 imidazo[4,5-*c*][1,5]naphthyridin-4-amine;  
a pharmaceutically acceptable acid;  
a water-miscible cosolvent; and  
a thickener system comprising a negatively charged thickener;  
wherein the aqueous gel has a viscosity of at least 1000 cps at 25°C.  
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2. An aqueous gel prepared by a method comprising combining components  
comprising:  
water;  
an immune response modifier (IRM) other than 1-(2-methylpropyl)-1*H*-  
15 imidazo[4,5-*c*][1,5]naphthyridin-4-amine, or a salt thereof;  
a water-miscible cosolvent; and  
a thickener system comprising a negatively charged thickener;  
wherein the aqueous gel has a viscosity of at least 1000 cps at 25°C.
- 20 3. The aqueous gel of claim 1 or claim 2 wherein the IRM in its free base form has an  
intrinsic aqueous solubility of less than 500 µg at 25°C.
4. The aqueous gel of claim 1 or claim 3 as dependent on claim 1 wherein the  
pharmaceutically acceptable acid is present in a stoichiometric amount relative to the IRM.
- 25 5. The aqueous gel of claim 1, claim 3 as dependent on claim 1, or claim 4 wherein  
the pharmaceutically acceptable acid is selected from the group consisting of an  
alkylsulfonic acid, an arylsulfonic acid, a carboxylic acid, a halo acid, sulfuric acid,  
phosphoric acid, a dicarboxylic acid, a tricarboxylic acid, and combinations thereof.
- 30 6. The aqueous gel of claim 5 wherein the acid is selected from the group consisting  
of acetic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, ethanesulfonic

acid, D-gluconic acid, D- and L-lactic acid, propionic acid, benzenesulfonic acid, citric acid, phosphoric acid, succinic acid, sulfuric acid, D- and L-tartaric acid, p-toluenesulfonic acid, and combinations thereof.

5 7. The aqueous gel of any one of claims 1 through 6 wherein the IRM is provided as a salt.

8. The aqueous gel of claim 7 wherein the IRM salt is a salt of an acid selected from the group consisting of an alkylsulfonic acid, an arylsulfonic acid, a carboxylic acid, a halo  
10 acid, sulfuric acid, phosphoric acid, a dicarboxylic acid, a tricarboxylic acid, and combinations thereof.

9. The aqueous gel of claim 8 wherein the IRM salt is a salt of an acid selected from the group consisting of hydrobromic acid, hydrochloric acid, methanesulfonic acid,  
15 ethanesulfonic acid, acetic acid, D-gluconic acid, D- and L-lactic acid, propionic acid, benzenesulfonic acid, citric acid, phosphoric acid, succinic acid, sulfuric acid, D- and L-tartaric acid, p-toluenesulfonic acid, and combinations thereof.

10. The aqueous gel of claim 8 wherein the IRM is an alkylsulfonate salt.  
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11. The aqueous gel of any one of claims 1 through 10 wherein the IRM is selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinolines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines; oxazoloquinoline  
25 amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazonaphthyridine amines; thiazolonaphthyridine amines; pyrazolopyridine amines; pyrazoloquinoline amines; tetrahydropyrazoloquinoline amines; pyrazolonaphthyridine amines; tetrahydropyrazolonaphthyridine amines; 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or  
30 tetrahydronaphthyridine amines; and combinations thereof.

12. The aqueous gel of any one of claims 1 through 11 wherein the IRM is selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinolines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines; and combinations thereof.
13. The aqueous gel of any one of claims 1 through 12 wherein the IRM is an imidazoquinoline amine.
14. The aqueous gel of any one of claims 1 through 13 wherein the IRM is 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine.
15. The aqueous gel of any one of claims 1 through 12 wherein the IRM is 2-propylthiazolo[4,5-*c*]quinolin-4-amine.
16. The aqueous gel of any one of claims 1 through 11 wherein the IRM is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, and imidazoquinoline diamines; amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline

amines, and tetrahydroimidazoquinoline diamines; amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, and thioether substituted imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; pyrazolopyridine amines; pyrazoloquinoline amines; tetrahydropyrazoloquinoline amines; pyrazolonaphthyridine amines; tetrahydropyrazolonaphthyridine amines; 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines; and combinations thereof.

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17. The aqueous gel of any one of claims 1 through 12 or 16 wherein the IRM is selected from the group consisting of amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, and imidazoquinoline diamines; amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, and tetrahydroimidazoquinoline diamines; amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted

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imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, and thioether substituted imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines;  
5 tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazonaphthyridine amines; thiazolonaphthyridine amines; 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines; and combinations thereof.

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18. The aqueous gel of claim 16 wherein the IRM is an amide substituted imidazoquinoline amine.

15 19. The aqueous gel of claim 18 wherein the IRM is selected from the group consisting of 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionamide, *N*-[2-(4-amino-7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]acetamide, and 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-propylbutyramide.

20 20. The aqueous gel of claim 19 wherein the IRM is *N*-[2-(4-amino-7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]acetamide.

21. The aqueous gel of claim 16 wherein the IRM is a urea substituted imidazoquinoline amine.

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22. The aqueous gel of claim 21 wherein the IRM is *N*-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]-*N'*-isopropylurea.

23. The aqueous gel of any one of claims 1 through 22 wherein the IRM is present in  
30 an amount of at least 0.0001 wt-%, based on the total weight of the aqueous gel.

24. The aqueous gel of any one of claims 1 through 23 wherein the water-miscible cosolvent is present in an amount of at least 10 wt-%, based on the total weight of the aqueous gel.
- 5 25. The aqueous gel of claim 24 wherein the water-miscible cosolvent is present in an amount of greater than 25 wt-%, based on the total weight of the aqueous gel.
26. The aqueous gel of any one of claims 1 through 25 wherein the water-miscible cosolvent is present in an amount of no greater than 90 wt-%, based on the total weight of  
10 the aqueous gel.
27. The aqueous gel of any one of claims 1 through 26 wherein the water-miscible cosolvent is selected from the group consisting of monopropylene glycol, dipropylene glycol, hexylene glycol, butylene glycol, glycerin, polyethylene glycol, diethylene glycol  
15 monoethyl ether, and combinations thereof.
28. The aqueous gel of claim 27 wherein the water-miscible cosolvent comprises monopropylene glycol.
- 20 29. The aqueous gel of any one of claims 1 through 28 wherein the thickener system further comprises a non-ionic thickener.
30. The aqueous gel of claim 29 wherein the non-ionic thickener is selected from the group consisting of hydroxyethyl cellulose, hydroxymethyl cellulose, and hydroxypropyl  
25 cellulose,
31. The aqueous gel of any one of claims 1 through 30 wherein the thickener system comprises at least two negatively charged thickeners of differing charge density.
- 30 32. The aqueous gel of any one of claims 1 through 31 wherein the negatively charged thickener comprises a cellulose ether, a polysaccharide gum, an acrylic acid polymer, or combinations thereof.



33. The aqueous gel of claim 32 wherein the thickener system comprises a polysaccharide gum and an acrylic acid polymer.

5 34. The aqueous gel of claim 33 wherein the ratio of polysaccharide gum to acrylic acid polymer is 1:20 to 20:1.

35. The aqueous gel of any one of claims 1 through 34 wherein the negatively charged thickener includes carboxylic acid and/or carboxylate groups.

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36. The aqueous gel of claim 35 wherein the thickener system comprises at least two negatively charged thickeners selected from the group consisting of carboxymethylcellulose sodium, xanthan gum, an acrylic acid polymer, and combinations thereof.

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37. The aqueous gel of any one of claims 1 through 36 wherein the thickener system is present in an amount of at least 0.1 wt-%, based on the total weight of the aqueous gel.

20 38. The aqueous gel of any one of claims 1 through 37 wherein the thickener system is present in an amount of no greater than 7 wt-%, based on the total weight of the aqueous gel.

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39. The aqueous gel of any one of claims 1 through 38 wherein water is present in an amount of at least 10 wt-%, based on the total weight of the aqueous gel.

40. The aqueous gel of any one of claims 1 through 39 further comprising a pharmaceutically acceptable pH adjusting agent.

30 41. The aqueous gel of claim 40 wherein the pharmaceutically acceptable pH adjusting agent is selected from the group consisting of hydrochloric acid, sodium hydroxide, tromethamine, potassium hydroxide, and combinations thereof.

42. The aqueous gel of any one of claims 1 through 41 further comprising a pharmaceutically acceptable buffer.

43. The aqueous gel of any one of claims 1 through 42 having a pH of 2 to 5.

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44. The aqueous gel of claim 43 having a pH of 3 to 4.

45. The aqueous gel of any one of claims 1 through 44 further comprising a preservative.

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46. The aqueous gel of claim 45 wherein the preservative is selected from the group consisting of quaternary ammonium compounds, benzethonium chloride, parabens, boric acid, isothiazolinone, organic acids, alcohols, carbamates, chlorhexidine, and combinations thereof.

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47. The aqueous gel of claim 46 wherein the preservative is selected from the group consisting of methylparaben, propylparaben, and combinations thereof.

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48. The aqueous gel of any one of claims 45 through 47 wherein the preservative is present in an amount of at least 0.005 wt-%, based on the total weight of the aqueous gel.

49. The aqueous gel of any one of claims 45 through 48 wherein the preservative is present in an amount of no greater than 1.0 wt-%, based on the total weight of the aqueous gel.

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50. The aqueous gel of any one of claims 1 through 49 further comprising a chelating agent.

51. The aqueous gel of claim 50 wherein the chelating agent is selected from the group consisting of ethylenediaminetetracetic acid, ethylenediaminetetracetic acid disodium salt, ethylenediaminetetracetic acid disodium salt dehydrate, and combinations thereof.

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52. The aqueous gel of claim 51 wherein the chelating agent is ethylenediaminetetraacetic acid disodium salt dihydrate.

53. The aqueous gel of any one of claims 50 through 52 wherein the chelating agent is present in an amount of at least 0.001 wt-%, based on the total weight of the aqueous gel.

54. The aqueous gel of any one of claims 50 through 53 wherein the chelating agent is present in an amount of no greater than 2.0 wt-%, based on the total weight of the aqueous gel.

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55. The aqueous gel of any one of claims 1 through 54 with the proviso that the negatively charged thickener is not covalently bonded to the IRM.

56. A method of delivering an IRM to mucosal tissue of a subject, the method comprising applying the aqueous gel of any one of claims 1 through 55 to the mucosal tissue.

57. The method of claim 56 wherein the mucosal tissue is associated with a condition selected from the group consisting of a cervical dysplasia, a papilloma virus infection of the cervix, a low-grade squamous intraepithelial lesion, a high-grade squamous intraepithelial lesion, atypical squamous cells of undetermined significance, a cervical intraepithelial neoplasia, an atopic allergic response, allergic rhinitis, a neoplastic lesion, and a premalignant lesion.

58. The method of claim 57 wherein the mucosal tissue is on the cervix and the associated condition is selected from the group consisting of cervical dysplasia, high-grade squamous intraepithelial lesions, low-grade squamous intraepithelial lesions, and atypical squamous cells of undetermined significance with the presence of high risk HPV.

59. The method of claim 58 wherein the mucosal tissue is on the cervix and the associated condition is atypical squamous cells of undetermined significance with the presence of high risk HPV.

60. The method of claim 57 wherein the mucosal tissue is on the cervix and the associated condition is a papilloma virus infection of the cervix.
- 5 61. The method of any one of claims 56 through 60 wherein the aqueous gel is applied to the mucosal tissue using a device selected from the group consisting of a barrel type applicator, a tampon, a cervical cap, a diaphragm, a cotton swab, a cotton sponge, a foam sponge, and a suppository.
- 10 62. The method of claim 61 wherein the device is a barrel type applicator.
63. The method of claim 62 wherein the barrel type applicator is prefilled.
64. A kit comprising a barrel type applicator and an aqueous gel of any one of claims 1  
15 through 55.
65. The kit of claim 64 wherein the kit includes a container separate from the applicator that includes the aqueous gel.
- 20 66. A method of inducing cytokine biosynthesis in a subject, the method comprising administering an aqueous gel of any one of claims 1 through 55 to the subject.
67. A method of treating a viral disease in a subject in need thereof, the method comprising administering an aqueous gel of any one of claims 1 through 55 to the subject.
- 25 68. A method of treating a neoplastic disease in a subject in need thereof, the method comprising administering an aqueous gel of any one of claims 1 through 55 to the subject.
69. A method of treating a dermal and/or mucosal condition in a subject in need  
30 thereof, the method comprising applying an aqueous gel of any one of claims 1 through 55 to the affected area of the subject.

70. The method of claim 69 wherein the dermal and/or mucosal condition is selected from the group consisting of herpes, keloids, warts, molluscum, or combinations thereof.

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